The American Journal of Medicine

The American Journal of Medicine

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Change of address must reach us one month preceding month of issue.

two
patients
with
angina pectoris

...your treatment can make *the difference*

In angina pectoris: ". . . the difference between complete, or almost complete, absence of symptoms, or a prolonged illness with much suffering" may lie in routine prophylaxis with Peritrate.[1]

New studies continue to confirm the effectiveness of this long-acting coronary vasodilator. "Impressive and sustained improvement" is observed in patients on Peritrate therapy.[2]

Simple prophylaxis: Peritrate is not indicated to abort the acute attack (nitroglycerin is still the drug of choice). However, you can reduce or eliminate nitroglycerin dependence and provide continuing protection against attacks of angina pectoris with Peritrate. Prophylaxis is simple: 10 or 20 mg. of Peritrate *before meals* and at bedtime. Maintenance of a continuous daily dosage schedule is important for successful therapy.

Peritrate has been demonstrated to prevent or reduce the number of attacks, lessen nitroglycerin dependence, improve abnormal EKG findings and increase exercise tolerance.[3,4,5]

The specific needs of most patients and regimens are met with Peritrate's five dosage forms: Peritrate 10 mg. and 20 mg. tablets; Peritrate Delayed Action (10 mg.) for continuous protection through the night; Peritrate with Phenobarbital (10 mg. with phenobarbital 15 mg.) where sedation is required; Peritrate with Aminophylline (10 mg. with aminophylline 100 mg.) in cardiac and circulatory insufficiency.

Usual Dosage: 10 to 20 mg. *before meals* and at bedtime.

References: 1. Rosenberg, H. N., and Michelson, A. L.: Am. J. M. Sc. *230*:254 (Sept.) 1955. 2. Kory, R. C., *et al.*: Am. Heart J. *50*:308 (Aug.) 1955. 3. Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1953. 4. Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952. 5. Dailheu-Geoffroy, P.: L'Ouest-Médical, vol. 3 (July) 1950.

Peritrate®

(brand of pentaerythritol tetranitrate)

WARNER-CHILCOTT

LEVOPHED®
in coronary
shock
saves 20 per cent more lives[1]

Among 131 patients in **severe** shock due to myocardial infarction, Levophed saved the lives of 53[1]—a remarkable salvage rate where ordinarily there is an 80 to 90 per cent mortality rate.[2]

Intravenously administered Levophed is almost **twice** as effective in relieving shock and saving lives as expectant treatment—transfusions and older pressor agents.[1] "Survival occurred in two fifths of patients treated with levarterenol [Levophed] and in only one fifth of patients treated expectantly."[1]

Because delay may be disastrous[3] Levophed should be used **first** and promptly.

Levophed raises blood pressure within 10 to 30 seconds—maintains it almost indefinitely. Unlike other agents, Levophed produces an increase in coronary blood flow and oxygen supply to the myocardium far in excess of the rise in mean blood pressure.[4] Levophed limits the size of the infarct and saves healthy myocardium.[5]

LEVOPHED
(levarterenol bitartrate)

natural antishock pressor hormone

1. Binder, M. J., et al.: **Am. Jour. Med.,** 18:622, Apr., 1955. **2.** Sampson, J. J.; and Zipser, Albert: **Circulation,** 9:38, Jan., 1954. **3.** Nichol, E. S., in Conn, H. F.: Current Therapy 1954. Philadelphia, W. B. Saunders Co., 1954, p. 196. **4.** Jamison, W. L., et al.: **Jour. Am. Geriat. Soc.,** 3:521, Aug., 1955. **5.** Gilchrist, A. Rae: **Brit. Med. Jour.,** 2:351, Aug. 16, 1952.

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CONTENTS

The American Journal of Medicine

Vol. XXI OCTOBER, 1956 No. 4

Editorial

Clinical Studies

A monothiol degradation product of penicillin, long familiar as penicillamine (β,β-dimethyl cysteine), was found to be a generally much more effective cupruretic agent than BAL in the treatment of Wilson's disease. Moreover, the new agent can be given orally. No toxic reactions were noted in the short term trials described. From Dr. Walshe's report it seems apparent that penicillamine deserves further study and not only in Wilson's disease but, as he points out, in the treatment of lead, gold and mercury poisoning.

Writing in the grand manner, the authors give what is perhaps the fullest available account of the clinical, laboratory and pathologic findings in that rare but intriguing cause of the nephrotic syndrome, renal vein thrombosis. They describe an illustrative case (with survival) from their own experience, giving in considerable detail the development of the course, including serial renal biopsies. The whole makes for interesting reading and constitutes a significant contribution to this subject.

Intravenous infusion of potassium salts, given in amounts and rates regulated by continuous electrocardiographic monitoring, abolished or suppressed a variety of supraventricular and ventricular arrhythmias in approximately three-fourths of cases, whether digitalis-induced or not. Potassium was found to be ineffective in controlling atrial flutter or fibrillation. While the results indicate that potassium infusion may have wider application in the management of certain common arrhythmias than generally appreciated, this form of therapy should not be indiscriminate or uncontrolled, particularly when there is impaired A-V conduction. The authors consider the physiologic as well as therapeutic implications of their observations.

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CONTENTS continued–October 1956

VOLUME TWENTY-ONE NUMBER FOUR

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NOW...

compounded for compatibility to assist you to individualize peptic ulcer therapy

NEW... TREVIDAL® LIQUID

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Calcium carbonate . .	105 mg.	Egraine®*	45 mg.
Magnesium trisilicate .	150 mg.	Regonol®+	35 mg.

Organon ORANGE, N. J.

*Binder from oat flour +Vegetable mucin

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VOLUME TWENTY-ONE NUMBER FOUR

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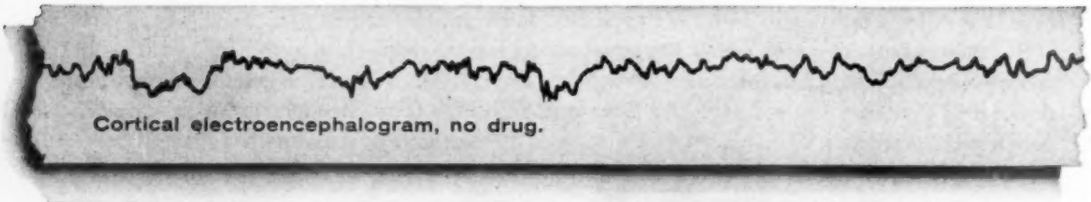
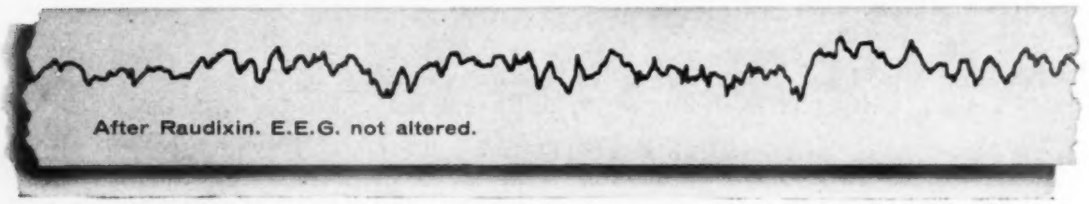
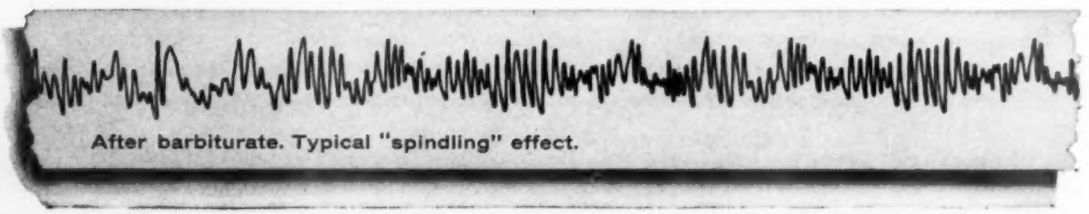
comparison of the effect of RAUDIXIN (tranquilizer) and a barbiturate (sedative)





Raudixin acts in the area of the midbrain and diencephalon and does not depress the cerebral cortex, as can be seen in this electroencephalogram. Consequently, the tranquilizing effect of Raudixin is generally free of loss of alertness.



Because barbiturates and other sedatives depress the cerebral cortex, as indicated by this "spindling," the sedation is often accompanied by a reduction in mental alertness.

RAUDIXIN

SQUIBB WHOLE ROOT RAUWOLFIA SERPENTINA

SQUIBB

DOSAGE: Usual initial dosage is 200 mg. daily. Maintenance dosage may be adjusted within a range of 50 mg. to 500 mg. daily, depending on the response observed and the possible appearance of side effects. Most patients can be adequately maintained on 100 mg. to 200 mg. per day. Because of its sustained action, Raudixin may be given in single daily doses if desired. *Note:* Tranquilizing action is usually evident in 3 to 10 days; for a more rapid onset of effect, the patient may be given a priming dose of 200 to 300 mg. twice daily for the first 3 days.

SUPPLY: 50 mg. and 100 mg. tablets, bottles of 100, 1000 and 5000.

CONTENTS continued–October 1956

VOLUME TWENTY-ONE NUMBER FOUR

Advertising Index on 3rd Cover

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Tetracycline *Lederle*

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[1]Posner, A. C., *et al.;* Further Observations on the Use of Tetracycline Hydrochloride in Prophylaxis and Treatment of Obstetric Infections, *Antibiotics Annual* 1954-55, pp. 594-598.

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References: 1. Gamble, J.R., et al. Arch. Int. Med. 95:52, 1955. 2. Gamble, J.R., et al. J. Lab. & Clin. Med. 42:805, 1953.

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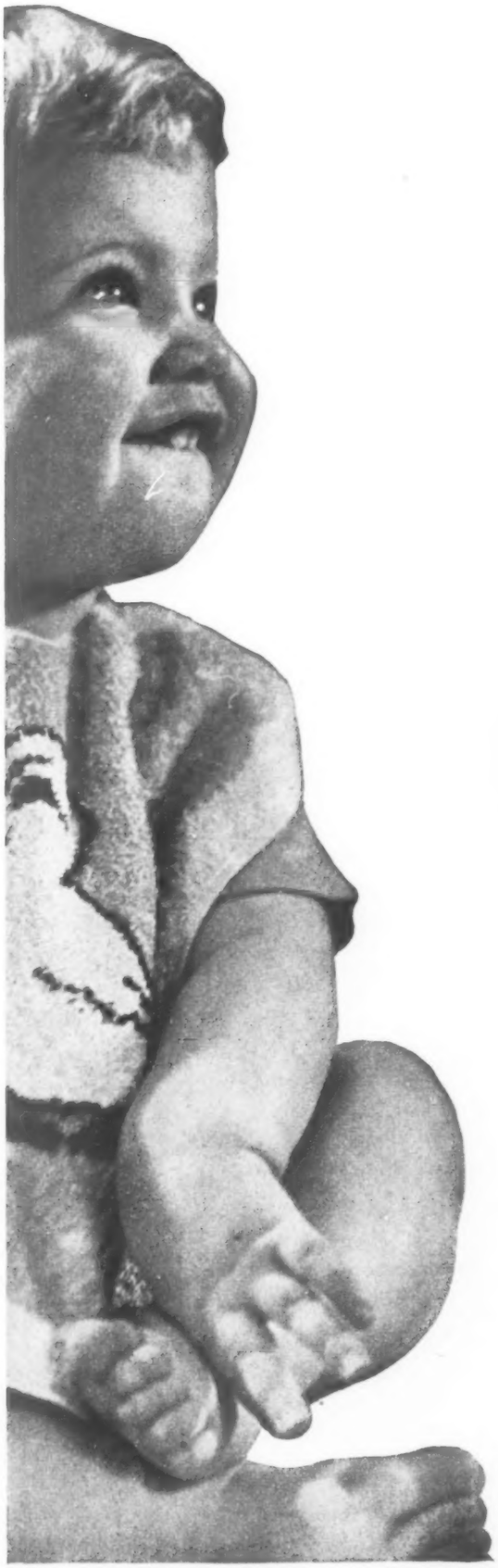
Xylocaine HCl Solutions are available in 2 cc. ampuls, 20 cc. and 50 cc. vials in strengths of 0.5%, 1% and 2%, with or without epinephrine.

Bibliography of approximately 300 Xylocaine references upon request.

*Southworth, J. L., and Dabbs, C. H.: Xylocaine: a superior agent for conduction anesthesia, Anesth. & Analg. *32*:159 (May-June) 1953.

Astra Pharmaceutical Products, Inc., Worcester 6, Mass.



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remedy
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appetite

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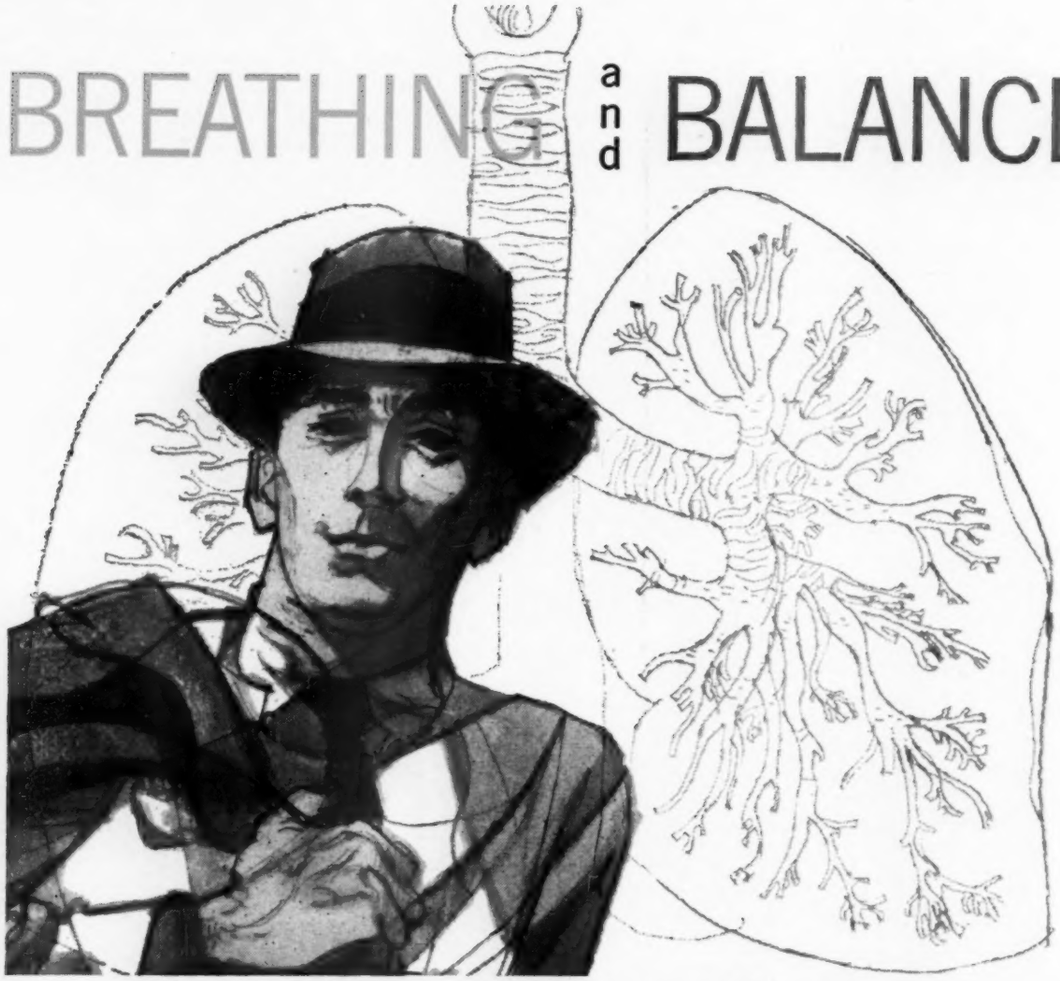

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one of "the best therapeutic agents now available"*

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*Schwartz, E.: New York J. Med. 56:570, 1956.

provides restoration of breathing capacity — Relief of symptoms [bronchospasm, cough, wheezing, dyspnea] is maintained for long periods with relatively small doses.*

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in specific
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nausea,
or constipation

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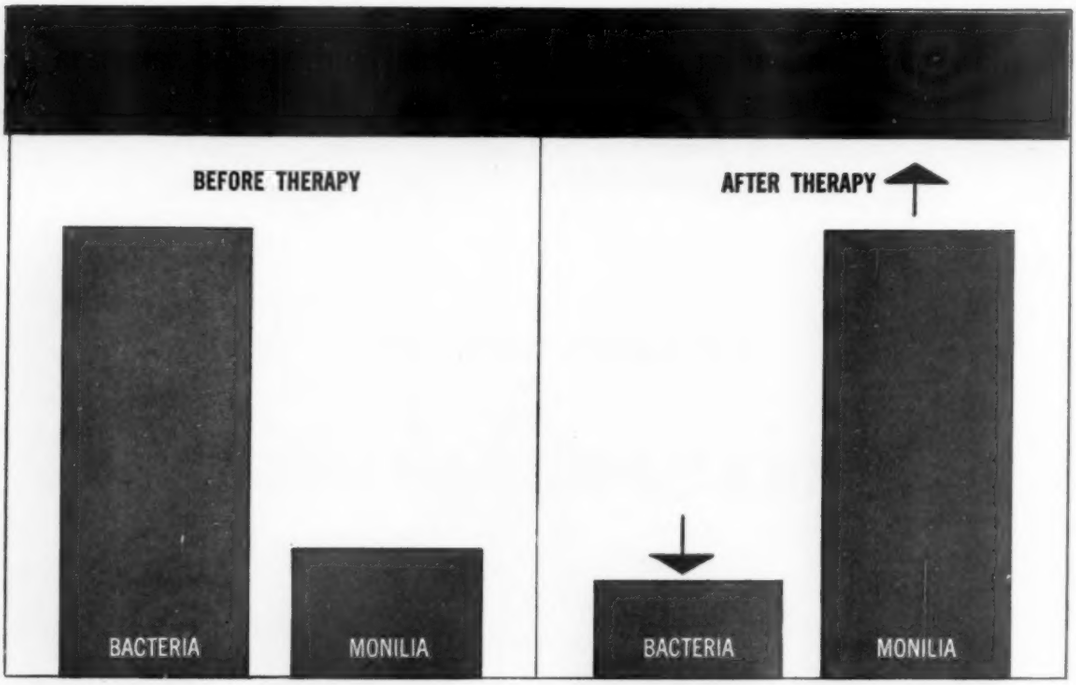

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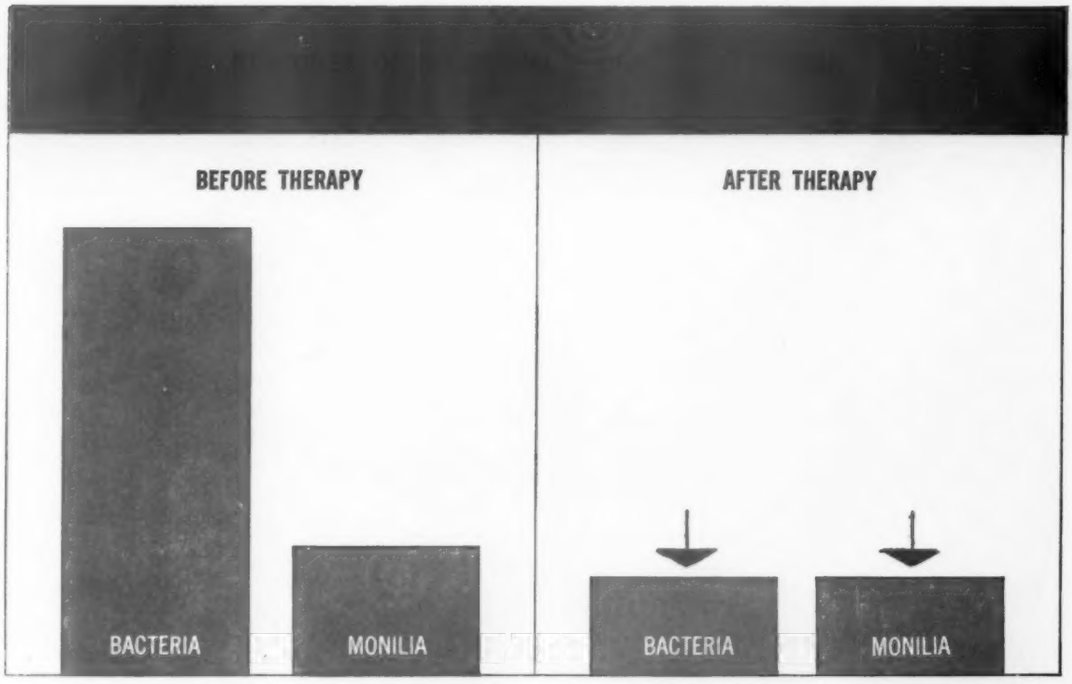

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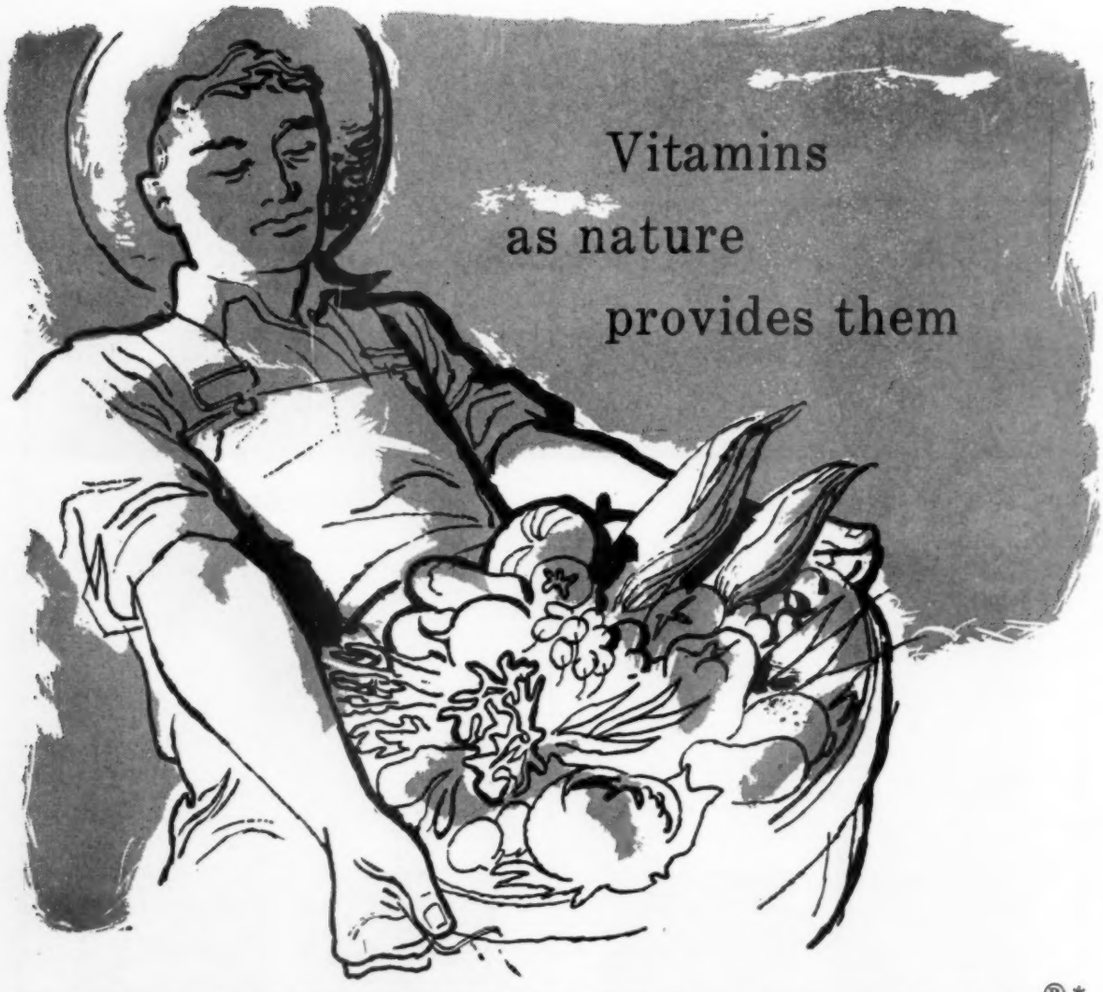
the only broad spectrum antibiotic preparation with added protection against monilial superinfection



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effective in minutes for hours (up to 6 hours with a single dose)
...does not induce rebound congestion
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**Menger, H. C.: New York J. Med. 56:1279, 1956*

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(end)

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1. Blank, P., and Boas, H.: Ann. West. Med. & Surg. 6:376, 1952.
2. Piper, C. E., and Nicklas, F. W.: Indust. Med. 23:510, 1954.

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When you want to control edema think first of

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A nonmercurial oral diuretic. Acts by inhibiting the enzyme carbonic anhydrase. Produces prompt, ample diuresis lasting from six to twelve hours. Morning dosage allows an uninterrupted night's sleep. Well-suited to long-term use. Nontoxic. The most widely prescribed drug of its kind!

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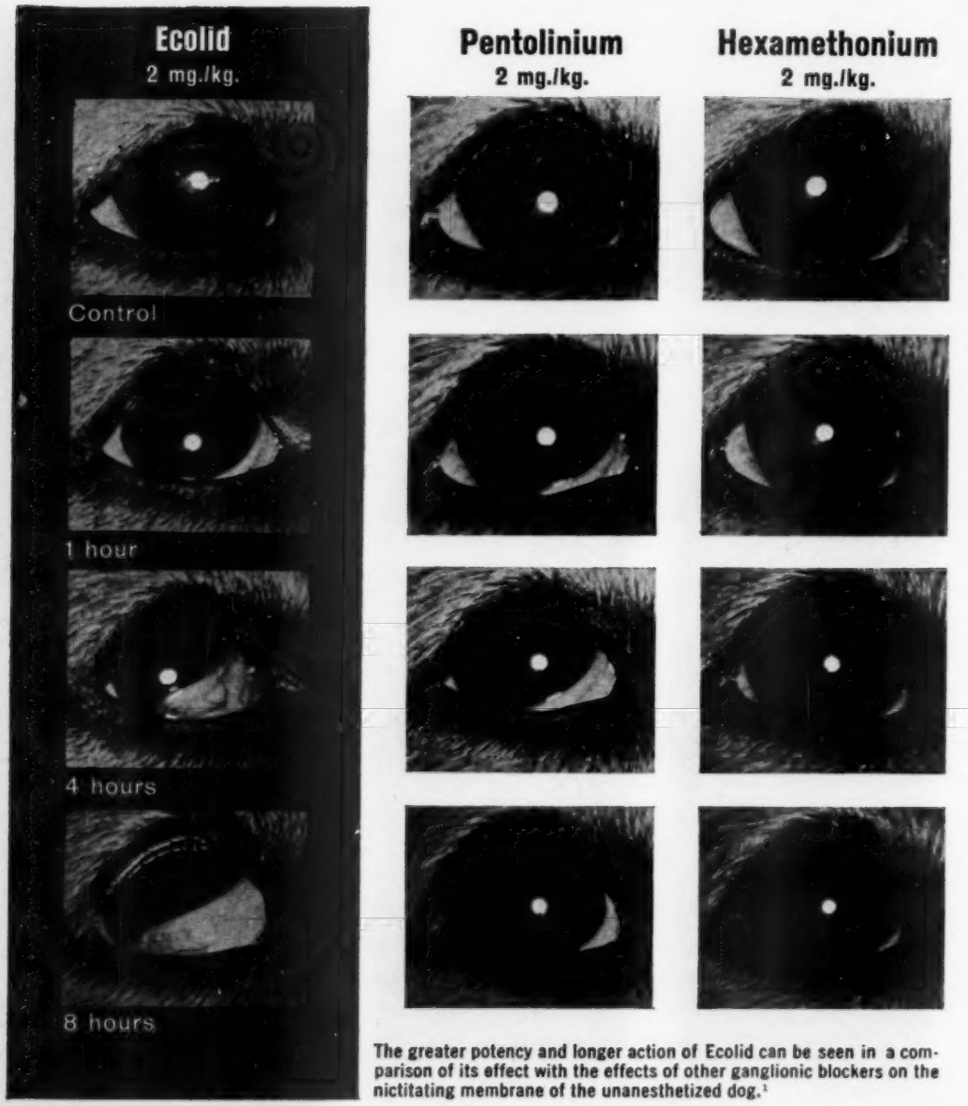
When less potent antihypertensives fail . . .



The greater potency and longer action of Ecolid can be seen in a comparison of its effect with the effects of other ganglionic blockers on the nictitating membrane of the unanesthetized dog.[1]

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*Pollack, H., and Halpern, S. L.: Therapeutic Nutrition, Washington, D. C., National Academy of Sciences—National Research Council, 1952, p. 21.

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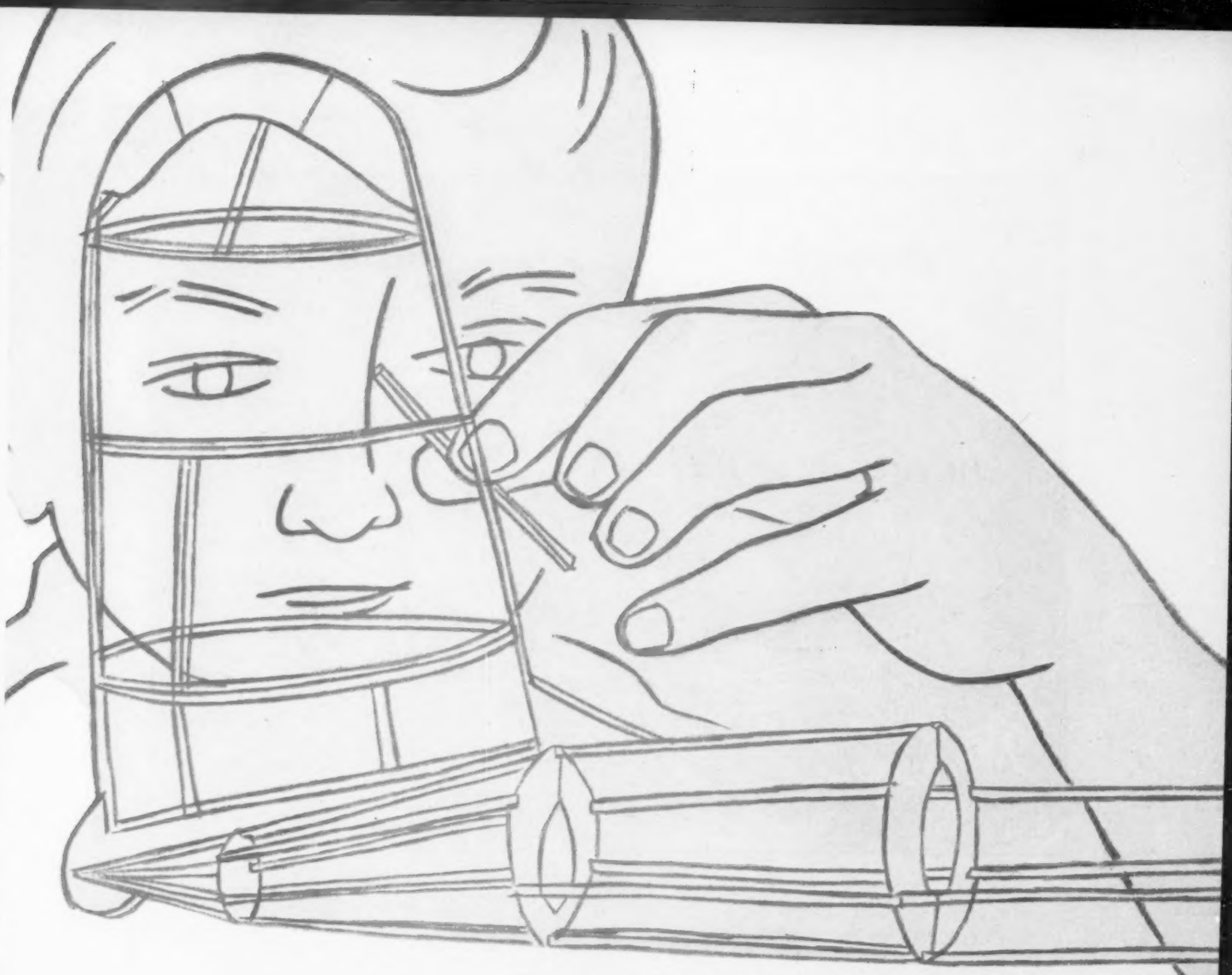

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(1) Zimmerman, F. T.: *New York J. Med.* 55:2338, 1955. (2) Drake, F. R.: *Am. J. M. Sc.* 230:98, 1955. (3) Levy, L., & Shanbrom, E.: *Arch. Int. Med.* 97:599, 1956.

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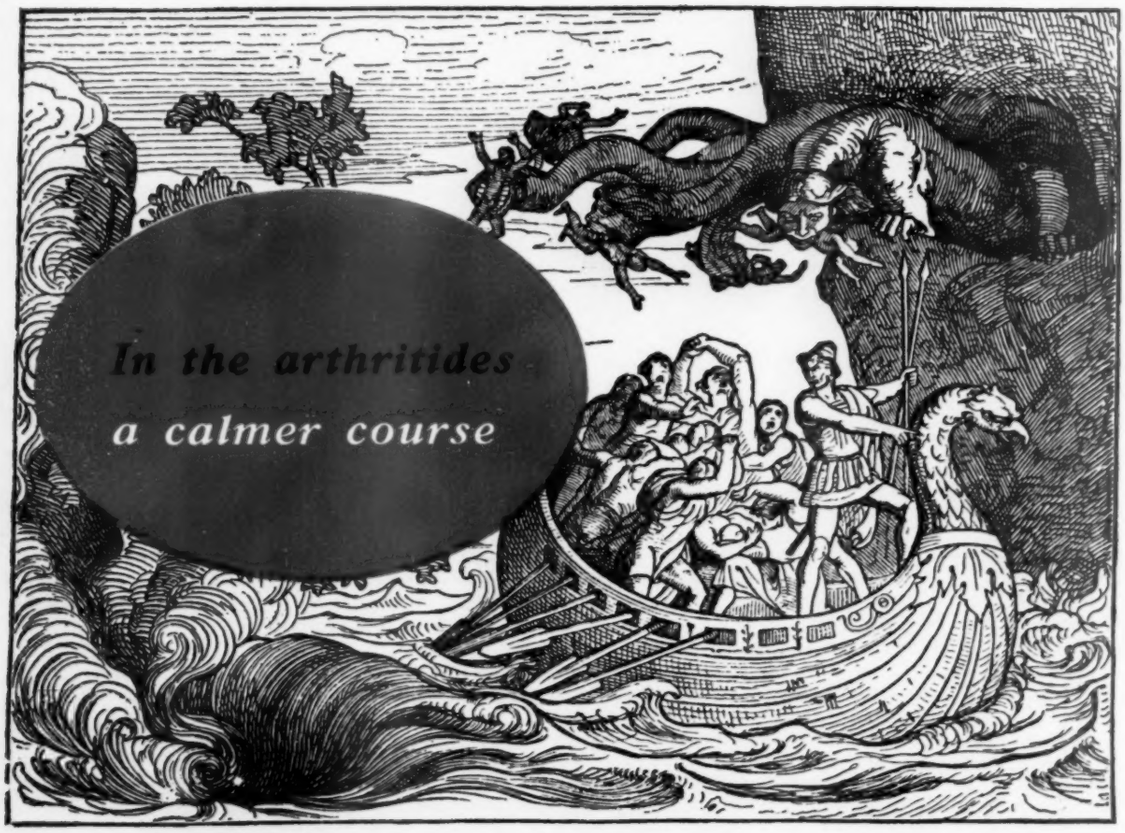

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[1]*Busse, E.A.: Treatment of Rheumatoid Arthritis by a Combination of Cortisone and Salicylates. Clinical Med.* 11:*1105*

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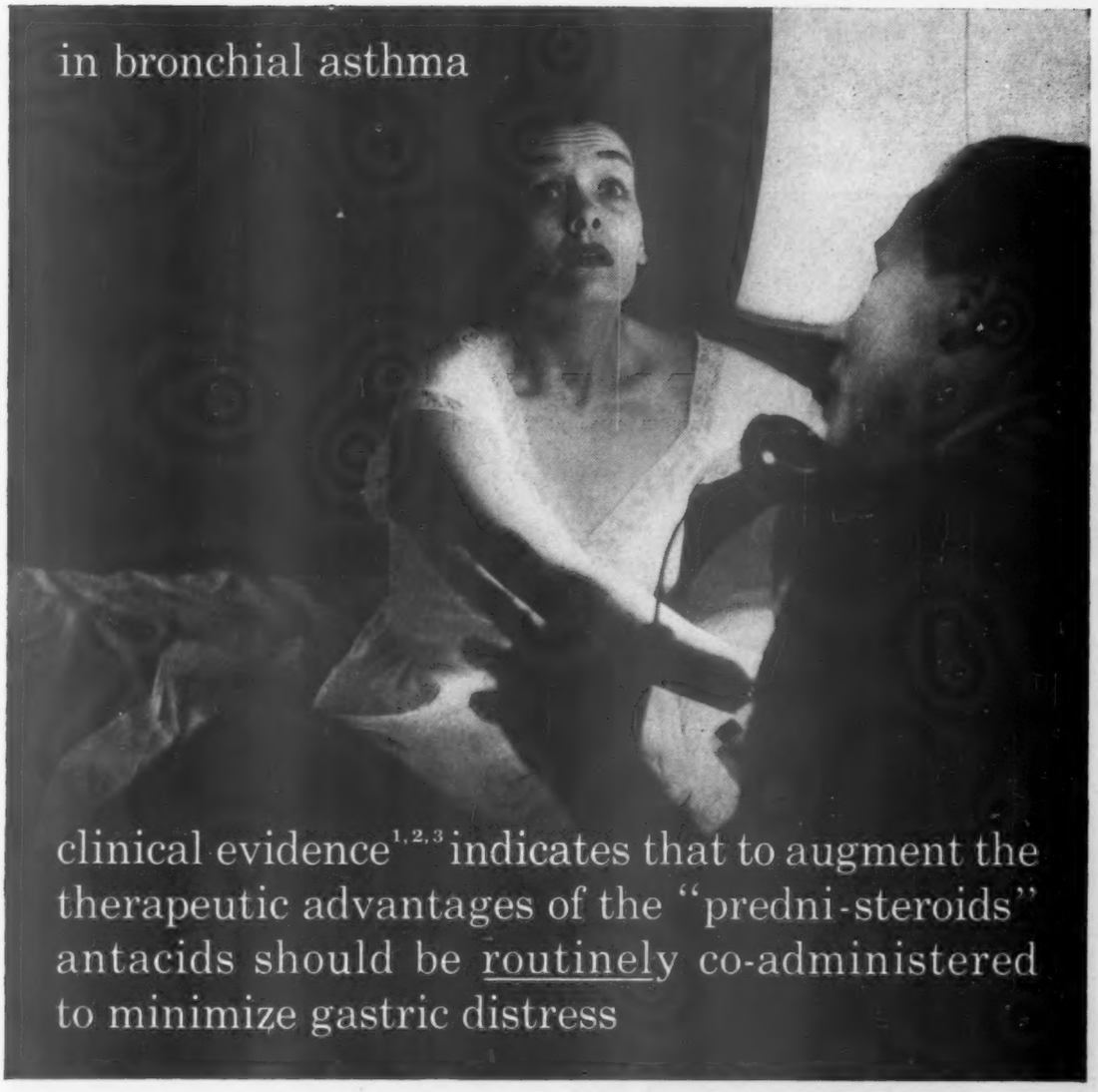

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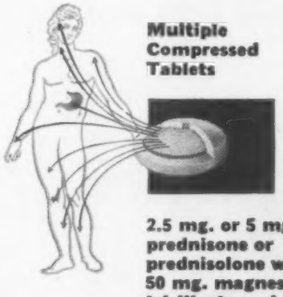

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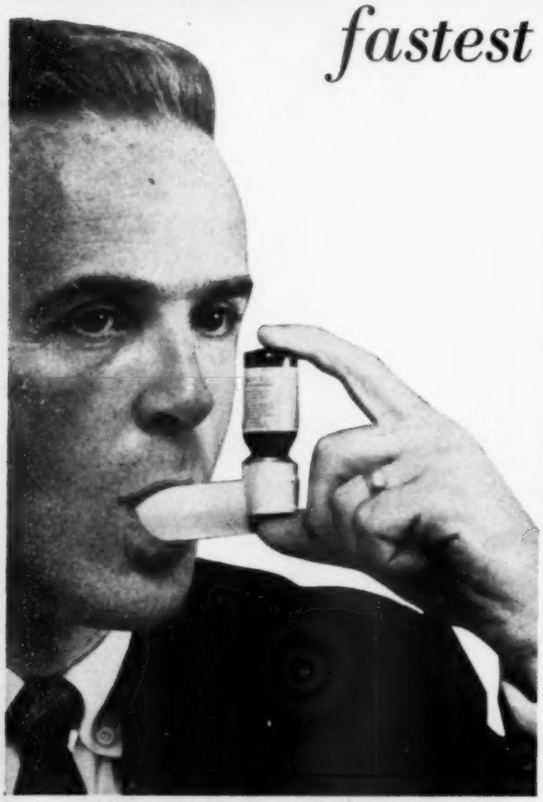

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"The really old people are those 10 years older than myself."[1]

"In the lay mind, anyone past 60 is ready for the discard . . ."[2]

". . . there are only three principal phases in the span of life: infancy, adolescence and senescence."[3]

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To the physician on the firing line of daily practice, the question of "how old is old?" seems academic. To him, a more valid question is "How can I allay the effects of the aging process?"

FIVE PROBLEMS IN AGING

The answer, according to most authorities, is manifold, for five treatable problems seem to predominate. One, obviously, is gonadal hormone decline. Another is mild anemia. A third is the decreased production of gastric and digestive enzymes. Mineral-vitamin deficiency is the fourth. And the fifth — perhaps most important — is inadequate high-quality protein intake.

THERAPY FOR AGING

Judging from this confused clinical picture of aging, therapy for the problem would appear difficult. However, most physicians agree that a product which could correct most or all of these five commonest problems would remove past obstacles to satisfactory response. Such a product would, essentially, be true "preventive geriatrics."

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new lysine, for protein improvement*

* Protein deficiency among the aging apparently stems from their excessive intake of white-flour foods which furnish incomplete protein of low biologic value. White bread protein, for example, has been shown by nutrition studies in animals[5] to be deficient only in the amino acid, lysine. In human subjects metabolic determinations indicate that the addition of supplemental lysine to a basal white-flour protein diet can convert a negative nitrogen balance into a positive one.[6]

A WORD ABOUT SYMPTOMATOLOGY

In spite of jokes to the contrary, the patient who states in the professional office that "old age is creeping up" is a rare bird indeed.

Seldom is old age the presenting complaint. Thus the physician, after correcting the specific complaints, must re-evaluate the whole person to judge his candidacy for "preventive geriatrics."

Such people have much to gain from NEOBON therapy. The rewards are fuller, more active, more pleasurable years for patients past 40. The daily dose (3 capsules) of NEOBON provides:

L-lysine	150 mg.
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Pancreatic Substance***	150 mg.
Glutamic Acid	90 mg.
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Vitamin A (Palmitate)	6,000 U.S.P. Units
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Thiamine Mononitrate (Vitamin B_1)	1.5 mg.
Riboflavin (Vitamin B_2)	1.5 mg.
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Niacinamide	150 mg.
Ascorbic Acid (Vitamin C)	150 mg.
Vitamin B_{12} (Oral Concentrate)	3 mcg.
Folic Acid	0.3 mg.
Liver-Stomach Substance**	300 mg.
Iron (from Ferrous Gluconate)	10.2 mg.
Cobalt (from Cobaltous Sulfate)	0.1 mg.
Molybdenum (from Sodium Molybdate)	2 mg.
Copper (from Cupric Sulfate)	1 mg.
Manganese (from Manganous Sulfate)	1 mg.
Magnesium (from Magnesium Sulfate)	6 mg.
Iodine (from Potassium Iodide)	0.15 mg.
Potassium (from Potassium Sulfate)	5 mg.
Zinc (from Zinc Sulfate)	1.2 mg.

**Enzymatically active defatted material obtained from 1,500 mg. whole fresh liver and stomach.

***Enzymatically active defatted material obtained from 750 mg. of whole fresh pancreas.

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Supplied: Bottles of 60 capsules, prescription only.

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Ferrous Gluconate	30 mg.
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Folic Acid	167 mcg.
Vitamin B_{12}	2.5 mcg.
l-Thyroxine	0.1 mg.
Ethinyl Estradiol	1 mcg.
Methyltestosterone	1 mg.
Liver Fraction I	25 mg.
Ethyl Alcohol	0.5 cc.

Dosage: One teaspoonful twice daily before meals, or as required.

Supplied: In 16 fluid ounce bottles, prescription only.

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Erythromycin in the treatment of osteomyelitis*

8/3/55

CASE SUMMARY

On 6/2/55, patient, male, age 28, fell on an old fracture and refractured the middle third of the right femur, superimposed on an old osteomyelitis.

On 7/7/55, the wound was saucerized and a hemolytic S. aureus (coag. +) was isolated from the osteomyelitis. Disc sensitivities were: penicillin, 10 units; erythromycin, 10 mcg.; tetracycline, 10 mcg.

On 7/15, the patient was placed on erythromycin therapy 400 mgm. q. 6. h. Patient afebrile after erythromycin started. X-rays showed evidence of healing with callus formation. No septicemia and clinical evidence indicates control of the infection.

On 8/3, the cast was removed and leg recast. Wound was in good condition with minimal drainage.

Diagnosis: fracture middle third of right femur, complicated by osteomyelitis.

Result: erythromycin aided healing of the old osteomyelitis and kept the infection under control.

*Communication to Abbott Laboratories

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References: 1. Boger, W. P., J. Amer. Ger. Soc. 3:553, Aug. 1955. 2. Lapin, J. H., Ann. Allergy 13:169, March-April 1955. 3. Ancelovan, M. B. and Fischbein, W. I., Antibiotic Med. 1:136, March 1955. 4. Statements of American Heart Association, Council on Rheumatic Fever and Congenital Heart Disease, Circulation 11: 317, Feb. 1955. 5. Miller, J. M. et al., Antibiotics Annual 1954-55, Medical Encyclopedia Inc., N.Y., p. 105. 6. Seal, J. R. et al., J. Lab. & Clin. Med. 44:831, Dec. 1954. 7. Martin, W. J. et al., Am. Pract. & Dig. Treat. 5:813, Oct. 1954. 8. Henner, R., Eye, Ear, Nose & Throat Monthly 33:530, Sept. 1954. 9. Rodstein, M. and Young, D., Clin. Med. 61:695, Sept. 1954. 10. Bernstein, S. J. et al., A. M. A. Arch. Int. Med. 93: 894, June 1954. 11. Craige, E., North Carolina M. J. 14:503, Dec. 1953. 12. Barach, A. L., J. Amer. Ger. Soc. 3:816, Sept. 1953. 13. Barach, A. L., Geriatrics 8:422, Aug. 1953. 14. Boger, W. P., Indus. Med. & Surg. 22:288, July 1953. 15. Young, D. and Rodstein, M., J.A.M.A. 152:987, July 1953. 16. Queries and Minor Notes, J.A.M.A. 152:1283, July 1953. 17. Roberts, E., A. M. A. Amer. J. Dis. Child. 85:643, June 1953. 18. Saint, W. W., J.A.M.A. 152:585, June 1953. 19. Hoang, R. R. and High, R. H., J. Pediat. 42:532, May 1953. 20. Antibiotics. Round Table Discussion, Pediatrics 11:270, March 1953. 21. Feinberg, B., Rhode Island M. J. 36:138, March 1953. 22. Flippin, H. P., Delaware State M. J. 25:55, March 1953. 23. Denny, F. W. Jr., Postgrad. Med. 13:153, Feb. 1953. 24. Flood, J. M., A. M. A. Arch. Dermat. & Syph. 67:42, Jan. 1953. 25. Kohn, K. H., Milzer, A. and MacLean, H., J.A.M.A. 151:347, Jan. 1953. 26. Siegal, S. et al., J. Allergy 24: 1, Jan. 1953. 27. Statements of American Heart Association, Council on Rheumatic Fever and Congenital Heart Disease, J.A.M.A. 151:141, Jan. 1953. 28. Keefer, C. S., Pennsylvania M. J. 55:1177, Dec. 1952. 29. Kerrell, W. E., J.A.M.A. 150:1450, Dec. 1952. 30. Levy, D. F., Connecticut State M. J. 16:899, Dec. 1952. 31. Romansky, M. J. and Kelser, G. A., J.A.M.A. 150: 1447, Dec. 1952. 32. Thomas, L., Minnesota Med. 35: 1105, Dec. 1952. 33. Jones, C. C., J. Iowa M. Soc. 42: 533, Nov. 1952. 34. Reimann, H. A. Postgrad. Med. 12:255, Sept. 1952. 35. Bunn, P. A., N. Y. State J. Med. 52:2005, Aug. 1952. 36. Finland, M. New England J. Med. 247:557, Oct. 1952. 37. Babione, R. W. et al., U. S. Armed Forces M. J. 3:973, July 1952. 38. Hansen, A. E., South. M. J. 45:423, May 1952. 39. Dowling, H. F., G. P. 5:53, Feb. 1952. 40. Rhoades, P. S., G. P. 5:67, Feb. 1952. 41. Dowling, H. F. and Lepper, M. H., Med. Clin. North Amer., Jan. 1952, p. 247. 42. Karelitz, S. and Schifrin, N., Postgrad. Med. 11:17, Jan. 1952. 43. Panel Discussion, Pennsylvania M. J. 55:42, Jan. 1952. 44. Flippin, H. F. et al., J.A.M.A. 147:918, Nov. 1951. 45. Massell, B. F., Mod. Concepts Cardiovas. Dis. 20:105, Sept. 1951. 46. Weinstein, L., Boston Med. Quarterly 2:1, Sept. 1951. 47. Massell, B. F. et al., J.A.M.A. 146:1469, Aug. 1951. 48. Finland, M., Bull. New York Acad. Med. 27:199, April 1951. 49. Wheatley, D., Brit. M. J. 1: 703, March 1951. 50. Keefer, C. S., Postgrad. Med. 9:101, Feb. 1951. 51. Bunn, P. A. et al., J.A.M.A. 144: 1540, Dec. 1950. 52. Weinstein, L. and Perrin, T. S., J. Pediat. 47:844, Dec. 1950. 53. Keefer, C. S., Am. J. Med. 7:216, Aug. 1949. 54. Robinson, J. A., Hirsch, H. L. and Dowling, H. F., Am. J. Med. 4:716, 1948. 55. Barach, A. L. and Garthwaite, B., Ann. Allergy 5: 297, Aug. 1947. 56. Herreld, R. D., J. Urol. 57:897, May 1947. 57. White, H. J., Lee, M. E. and Alverson, C., Proc. Soc. Exper. Biol. & Med. 62:35, 1946. 58. Baumann, F. et al., J. Allergy 17:264, Sept. 1946. 59. Gamble, T. O. et al., Am. J. Obst. & Gynec. 50: 514, Nov. 1945. 60. Woofter, A. C. and Hoffman, O. E., J. Iowa M. Soc. 35:189, May 1945.

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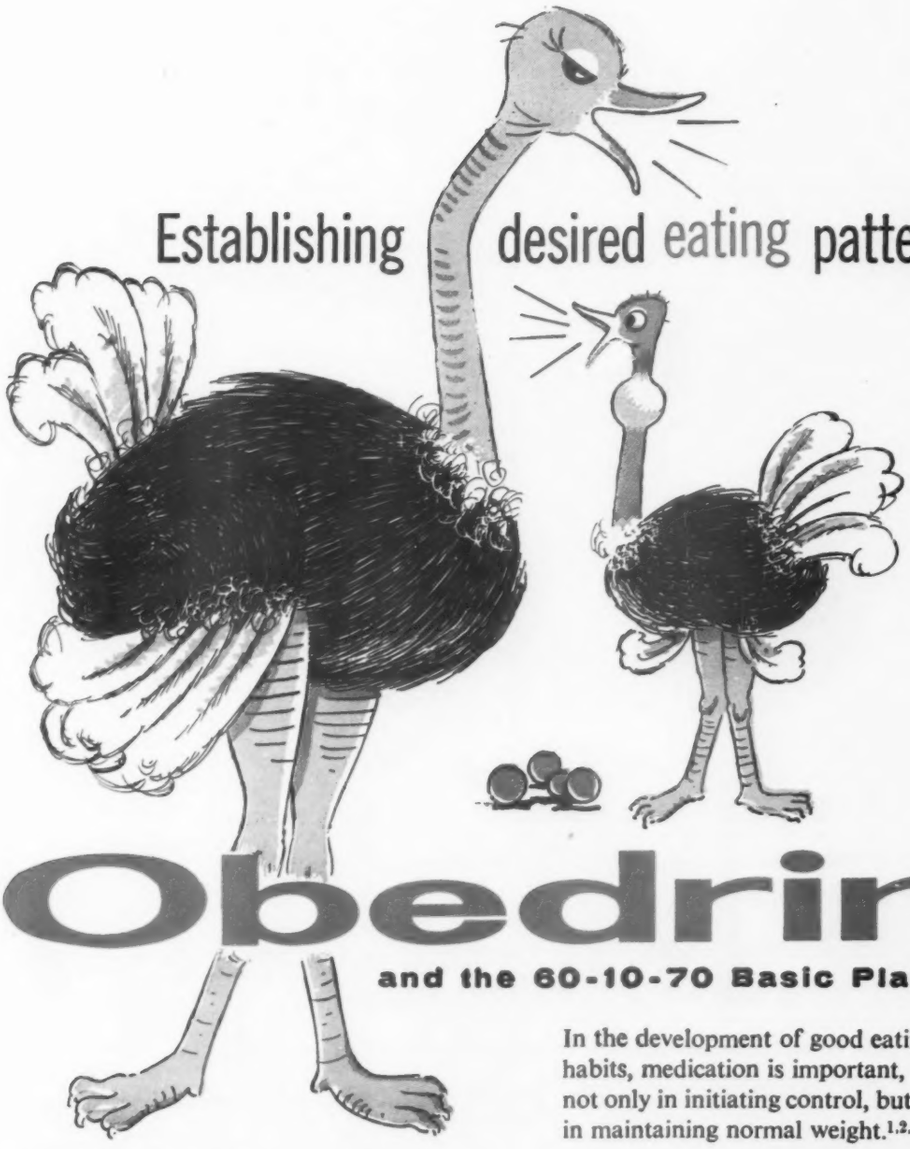

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1. Eisfelder, H.W.: Am. Pract. & Dig. Treat., 5:778 (Oct.) 1954).
2. Sebrell, W.H., Jr.: J.A.M.A., 152:42 (May, 1953).
3. Sherman, R.J.: Medical Times, 82:107 (Feb., 1954).

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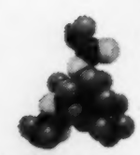

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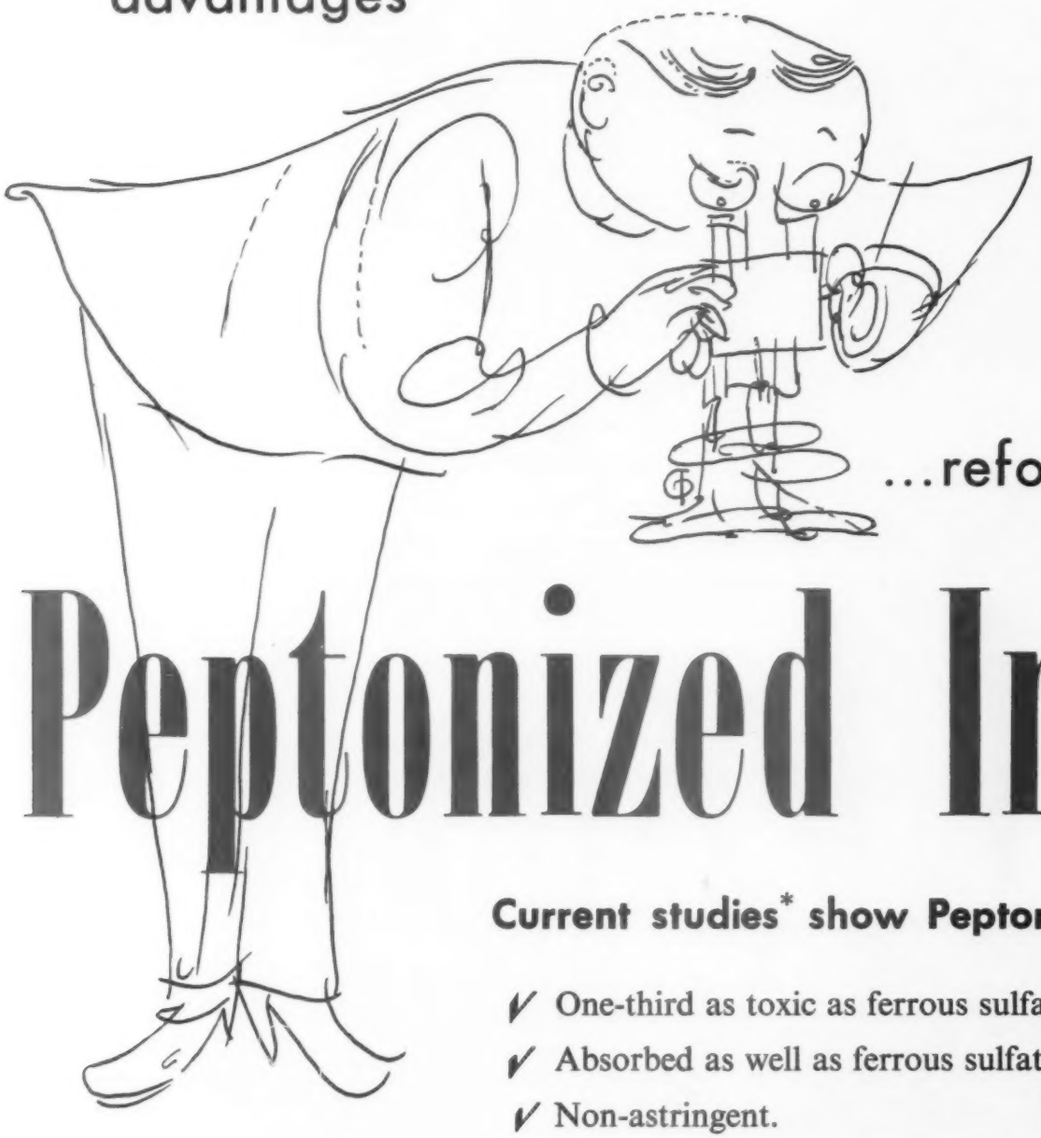

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*Keith, J. H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Read before the American Association for the Advancement of Science, Zoological Section, Atlanta, Georgia, December, 1955.

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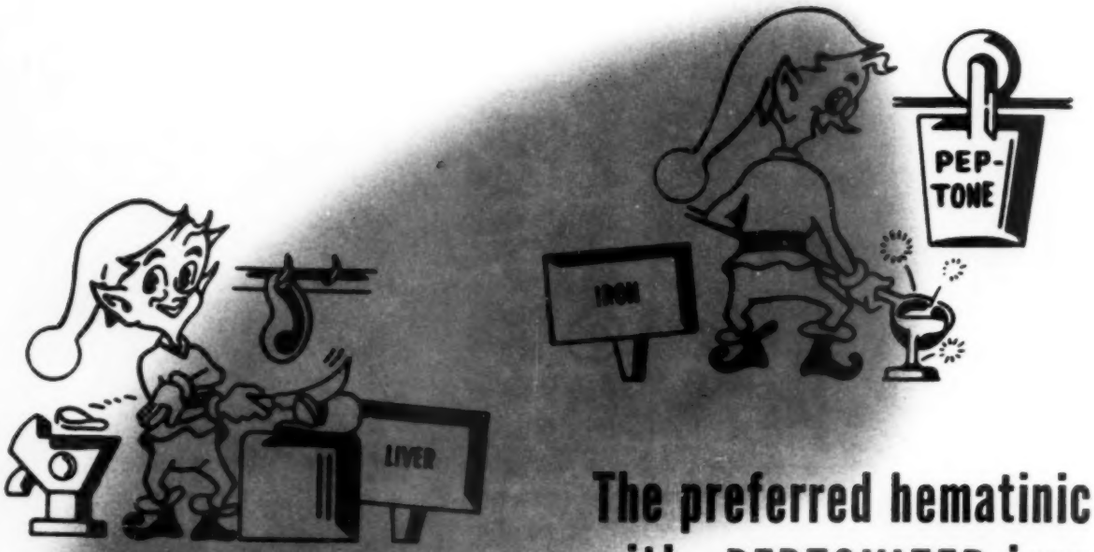

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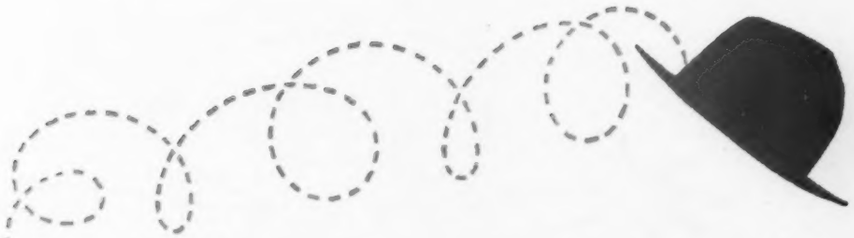

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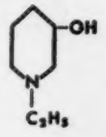

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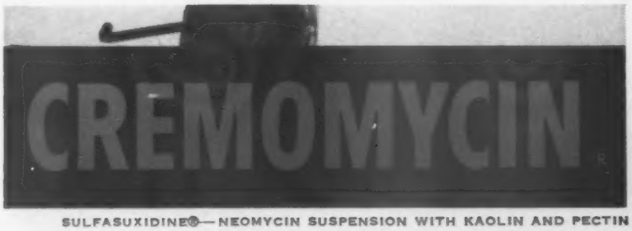

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Supplied in 16-ounce and 1-gallon bottles.

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Ammonium chloride	8 gr.
Potassium guaiacolsulfonate	8 gr.
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In RENIR, the action of reserpine is counterbalanced by small doses of ephedrine. Investigators state that "these two drugs act together to give a true synergistic response in that the untoward effects of each are counteracted and the desirable therapeutic effects of each are enhanced." They add that "ephedrine, in the small doses indicated . . . did not interfere with the hypotensive action."[1]

Indications: In the treatment of mild, moderate and labile hypertension. Also anxiety and tension states; mild to severe neurosis.

Suggested Dosage: For hypertension, 1 to 3 tablets daily. As a tranquilizer in mentally disturbed states, 2 to 4 tablets daily.

Supplied: Tablets containing reserpine 0.25 mg., and ephedrine 8.0 mg., in bottles of 100 and 1000.

Contraindications: To be used with caution in patients with peptic ulcer, mental depression, cardiac conditions and related disorders.

Literature and Samples on Request

[1]Feinblatt, T.M., Feinblatt, H.M., and Ferguson, E.A.: Rauwolfia-Ephedrine, As a Hypotensive-Tranquilizer. J.A.M.A. *161*:424 (June 2, 1956).

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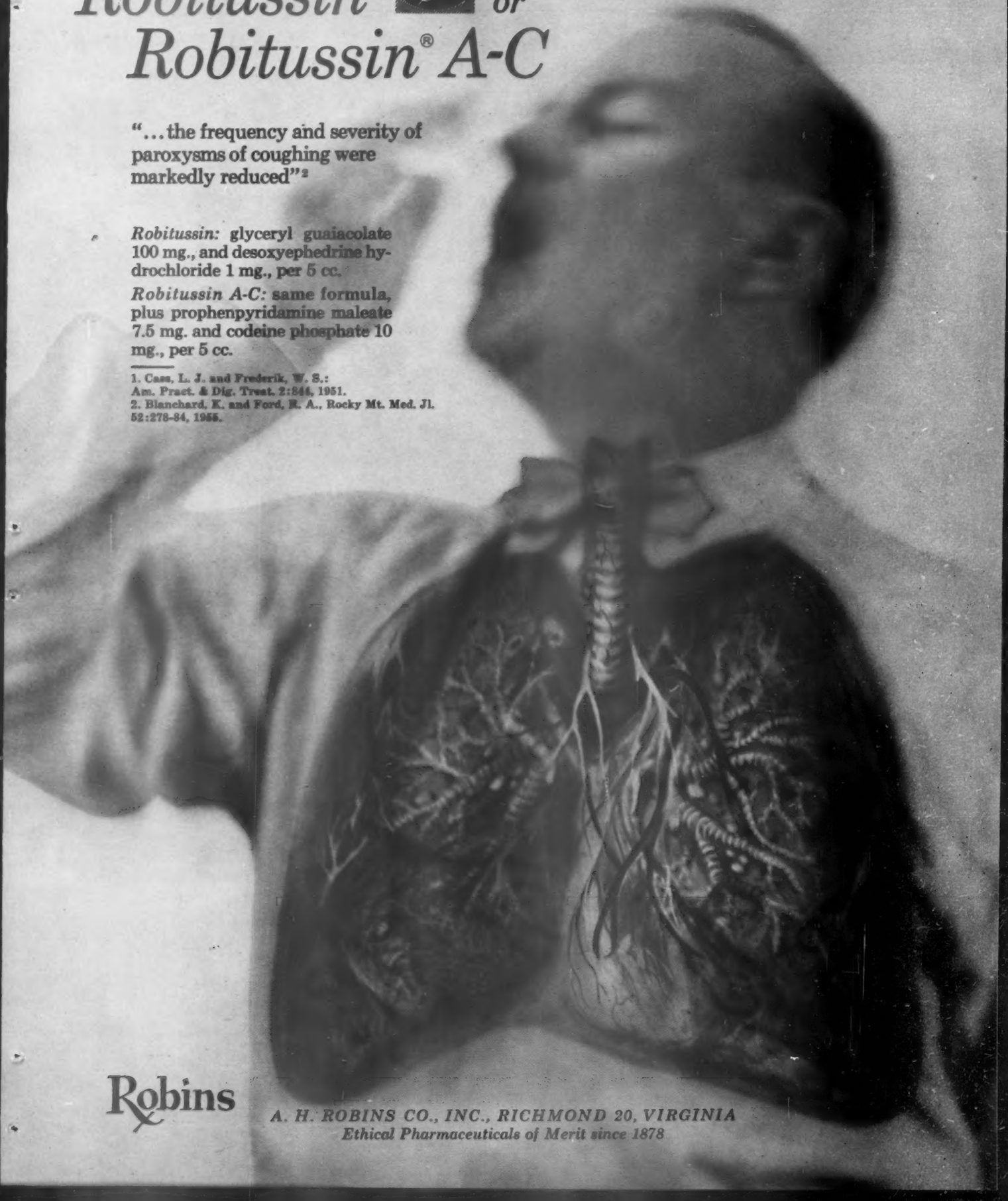
Robitussin® or *Robitussin*® *A-C*



"...the frequency and severity of paroxysms of coughing were markedly reduced"[2]

Robitussin: **glyceryl guaiacolate 100 mg., and desoxyephedrine hydrochloride 1 mg., per 5 cc.**

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1. Cass, L. J. and Frederik, W. S.: Am. Pract. & Dig. Treat. 2:844, 1951.
2. Blanchard, K. and Ford, R. A., Rocky Mt. Med. Jl. 52:278-84, 1955.

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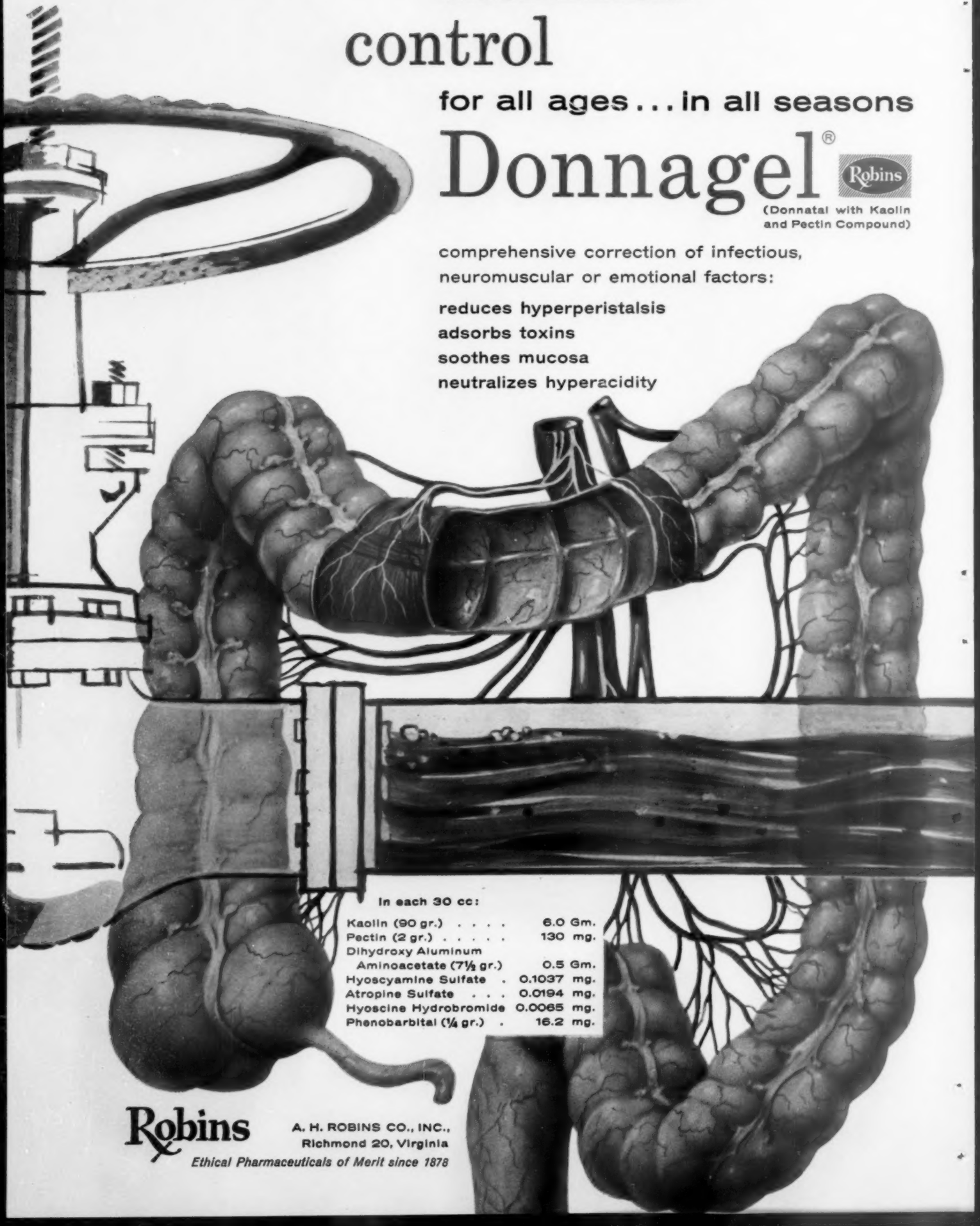

In each 30 cc:

Kaolin (90 gr.)	6.0 Gm.
Pectin (2 gr.)	130 mg.
Dihydroxy Aluminum Aminoacetate (7½ gr.)	0.5 Gm.
Hyoscyamine Sulfate	0.1037 mg.
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Hyoscine Hydrobromide	0.0065 mg.
Phenobarbital (¼ gr.)	16.2 mg.

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The investigators report on a total of 109 cases of herpes zoster and 313 cases of neuritis, all of whom were seen in private practice. All but one patient in each category responded with complete recovery.

This significant response is attributed to the fact that Protamide therapy was started promptly at the patient's first visit.

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Each tablet contains:

Aminophylline	5.0 gr.
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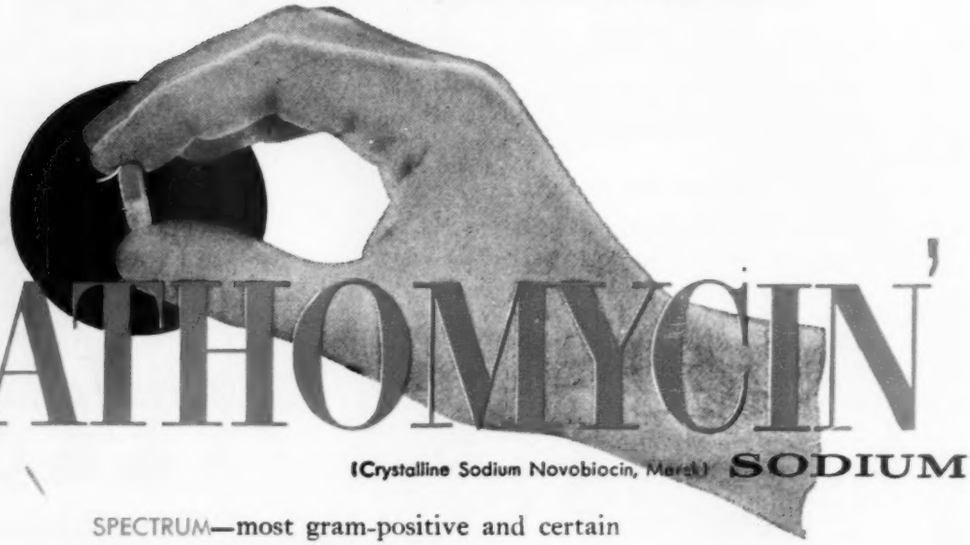

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DOSAGE—Two capsules (500 mg.) twice daily or one capsule (250 mg.) four times a day.

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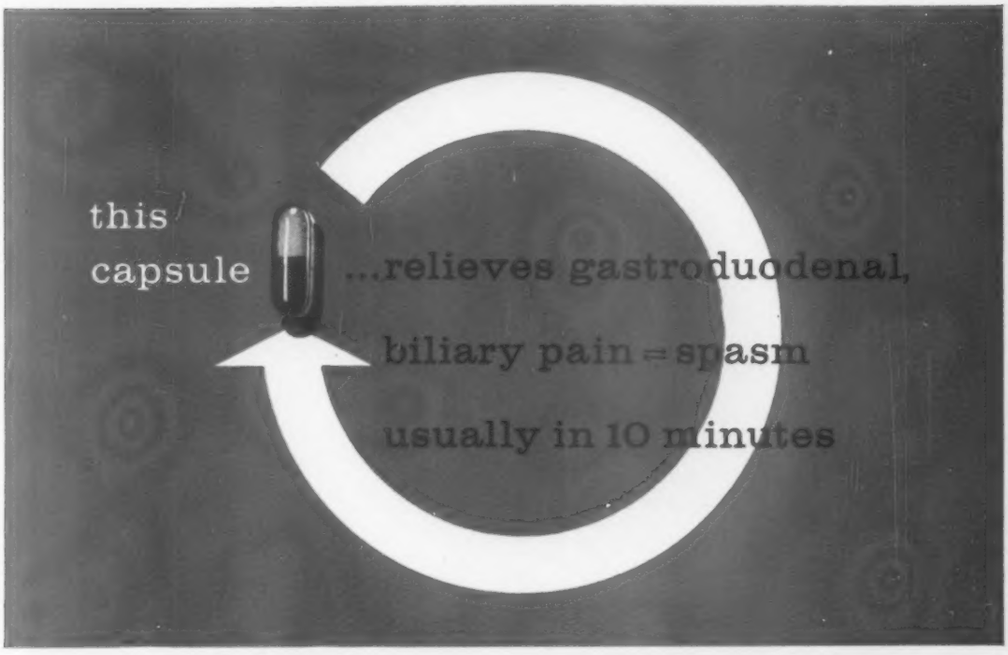

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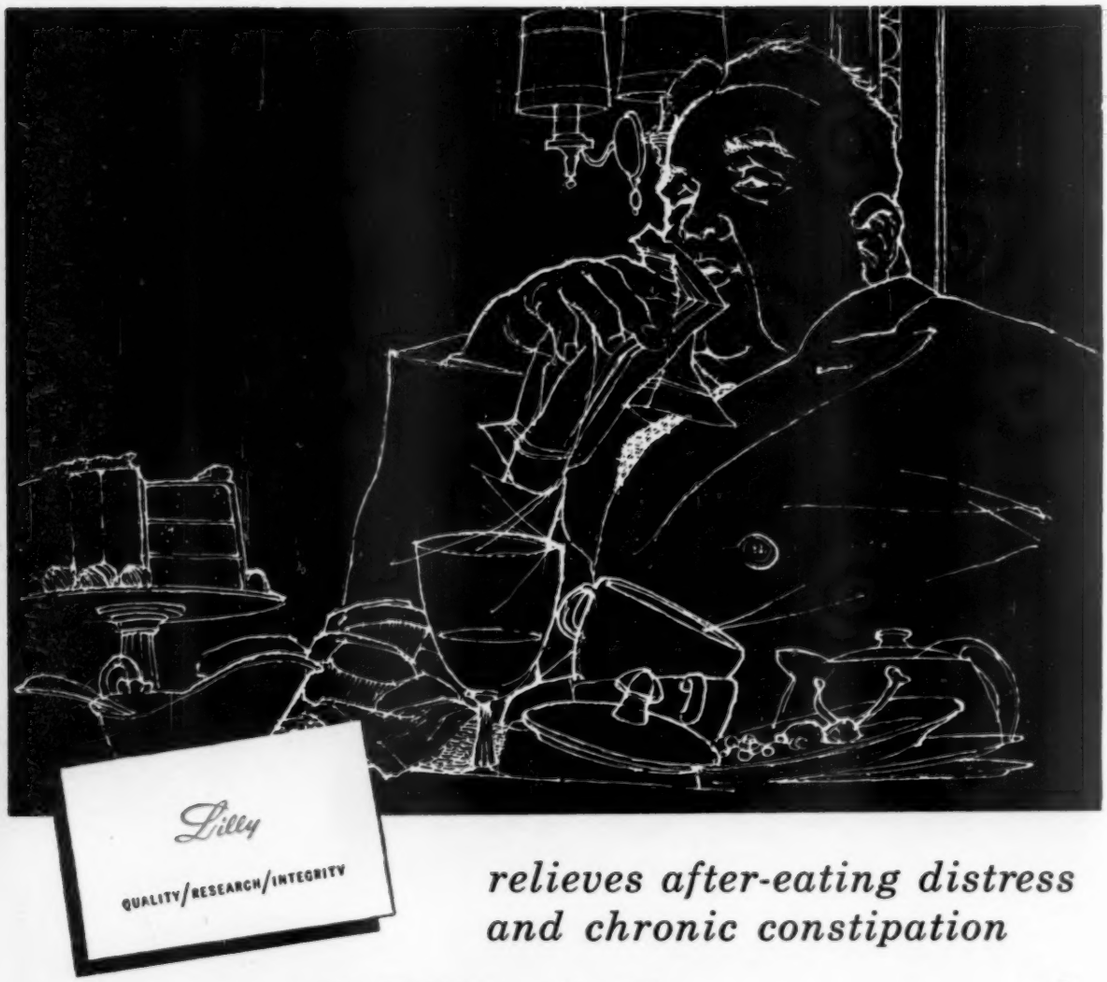

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The American Journal of Medicine

VOL. XXI OCTOBER, 1956 No. 4

Editorial

The Autopsy Room As a Hall of Learning

IT has become fashionable, in the name of "fundamental research," to devaluate, even to deride the autopsy. The school of Virchow is being borne to Golgotha by those who know not what they do.

What is the school of Virchow? It is least known to those who decry it most. Perhaps it can best be described in the words of the founder himself. At the age of twenty-six we find him lamenting, in the preface of the first volume of his Archiv, "that, for decades, physiology has been a stranger to medicine," and asserting that "pathological physiology is the main framework of scientific medicine, upon which pathological anatomy and clinical practice are only frills."[1] With time, this conviction grew and it is reiterated in the preface to the hundredth volume, almost forty years later.[2] And as regards Virchow's appreciation of mind as well as matter: "Let no physiologist, and no practitioner, forget that medicine units within itself all knowledge of the laws which govern the body and the soul."[3] William Henry Welch, another great pathologist and the Prometheus of scientific medicine in this country, quoted, in an obituary, Virchow's dictum: "Observe, experiment; seek the aid of allied sciences, chemistry, physics, general biology; collect by systematic and purposeful investigation, in which the 'Fragestellung' is correct and clear, a body of facts, and from this deduce general principles and laws."

Modern pathology may thus be paraphrased as investigative medicine, not simply the study of the morphology of diseased organs as some poorly informed practitioners proclaim. The practice of medicine and surgery represents the application of pathology to the care of patients. It is pathology that is the mother science—now, as in the time of Virchow.

The teachers in pathology of the present generation of professors, some of whom are vigorously at work today, have abided by these principles; to suggest that they glorified morphology and that "experiment was alien to almost all of them"[4] is simply not consonant with the facts. On the contrary, these great teachers performed and stimulated an enormous amount of experimental work. It is nothing new, in fact a routine practice in a well regulated autopsy service, to use the material for developing new procedures and for experiments. Hearts were revivified and their functions studied more than a quarter of a century ago.[5] This "potential value of the autopsy today" has indeed long been realized! When the great teachers were moved to inscribe on the walls of the morgue 'Hic locus est ubi mors gaudet succurere vitae," it was meant to inspire humility in those who came to learn. And those who come, including some outstanding professors of clinical medicine, still learn much; it is only those who come not that say there is no more to learn! And for those armed with the newer knowledge of chemistry and physiology there is even more to learn from the "routine autopsy" than there ever has been in the past.

Now, there are those who have applauded the degradation that has recently occurred in some

[1] VIRCHOW, R. Ueber die Standpunkte in der wissenschaftlichen Medicin. *Virchow's Arch.*, 1: 1–19, 1847.

[2] VIRCHOW, R. Der hundertste Band des Archivs. *Virchow's Arch.*, 100: 1–15, 1885.

[3] VIRCHOW, R. Die naturwissenschaftliche Methode und die Standpunkte in der Therapie. *Virchow's Arch.*, 2: 1–37, 1849.

[4] STARR, I. Potential values of the autopsy today. *J. A. M. A.*, 160: 1144–1145, 1956.

[5] WEARN, J. T. The role of the Thebesian vessels in the circulation of the heart. *J. Exper. Med.*, 47: 293–316, 1928.

departments of what was once the four-legged chair of Pathology, supported by investigation, teaching, service and administration, into a shapeless stool holding itself up on a single, often flimsy stick of "fundamental research." These hurrahs for the professional amputees who have divested themselves of interest in autopsies are shouted with a notable lack of logic when, with another breath, it is asserted that autopsies are, of course, invaluable for teaching medical students, if not others. Is it asking too much of teachers in medical schools that they teach school? Should irresponsibility be considered a virtue?

The pathogenesis of the atrophy, or even necrosis, that has befallen some departments of pathology is not difficult to understand. In a position where few can dispute his activities the temptation is high for the professor to pursue his interests undisturbed, and to enjoy the garlands showered upon the successful investigator. On the contrary, the conduct of an autopsy service that is useful for investigation and teaching is often attended with more complaints than kudos, and is certainly burdensome and time-consuming. The professor, then, finds it very convenient to relinquish responsibility for the autopsy service. It is precisely in such institutions that " . . . as far as the autopsies are concerned, things seem to be at the nadir," and that the "audacity and mental caliber of the personnel doing the autopsies have declined."[4] But it must be emphasized that this is a local phenomenon, to be observed where the professor neglects the autopsy room and permits it to become an insignificant appendage to the underbelly of the hospital. Then the practitioners themselves lose interest in a poor service that is grudgingly conducted in routine fashion by the unsupervised, unstimulated and unskilled. Moreover, when the professor of pathology has thus isolated himself from the main stream of human biology in disease he can no longer address the clinicians in their own terms. It is small wonder, then, that under such conditions the clinical-pathologic conferences also cease to be stimulating or even informative.

On the other hand, a well conducted autopsy service not only provides a vital source of material for chemical as well as anatomic studies and an investigative tool (one of many in a modern department) but also constitutes a priceless, continuing and intimate contact with the natural history of disease. When the clinicians of the "modern" school caution against limiting the medical horizon to the microscopic field, pathologists must agree; but the lumen of a cardiac catheter provides an even more restricted field of vision and at less magnification! As a background for clinical medicine the years spent in a well conducted pathology laboratory can be immensely more valuable than a year in some highly restricted field of clinical investigation. For, in a modern department the functional approach prevails, experimental work is in active progress, even the cardiac catheter connected with appropriate recording equipment finds its uses; but, in addition, the autopsy service provides a vast panorama of disease, studied with skill and with humility, in correlation with the clinical and laboratory records, electrocardiograms, roentgen films and other sources of useful information. It is, of course, in such an atmosphere, using tools tried and true as well as new, that the pathologists of the coming generation must be permitted to educate themselves and to continue their education when they have attained their professorships. A good autopsy service is never "routine." It is as unthinkable that pathologists can be educated without this discipline, and the knowledge that it will impart and the thought that it should stimulate, as it would be to train house officers in clinical medicine without patients. It was to the immense advantage of past generations of professors of medicine that they availed themselves of the opportunity of serving a year or more in the department of pathology. Symptomatic of the lack of this education is the lamentable overspecialization that afflicts the teaching of some of those who occupy once-important chairs today. This is not to condemn competence and skill in a special field but to extol breadth of understanding. Certainly, these can co-exist in clinical medicine, as in pathology.

AVERILL A. LIEBOW, M.D.
Department of Pathology
Yale University School of Medicine
New Haven, Conn.

Clinical Studies

Penicillamine, a New Oral Therapy for Wilson's Disease*

J. M. WALSHE

London, England

AN increased concentration of copper in both the liver and brain of patients dying of Wilson's disease (hepatolenticular degeneration, H.L.D.) was noted by Haurowitz,[1] Lüthy[2] and Glazebrook.[3] These observations, all made on single cases, were confirmed and extended by Cumings[4] who reported a series of three patients who died of H.L.D. It is now known that, in addition to the excess copper in the tissues, there is an increased excretion of copper in the urine, a low plasma copper concentration and a very low level of ceruloplasmin, the copper-binding α globulin.[5] This last is believed to be the primary biochemical defect in Wilson's disease.

The removal of excess copper from patients with H.L.D. by the parenteral use of 2,3–dimercaptopropanol (BAL), $CH_2SH.CHSH.CH_2OH$, was first reported by Mandlebrote and Thompson[6] and has been confirmed by many subsequent workers. Given in repeated courses and over long periods of time BAL may lead to marked clinical improvement[7] although in the more acute forms of the disease the results are less satisfactory.[8,9] Intravenous versene® and amino acids have also been shown to increase the copper excretion,[8–10] as well as high protein diets and cortisone.[10] Absorption of copper from the intestine can be reduced by the oral administration of potassium sulphide[9] or carbo-resin.[11]

At present, parenteral administration of BAL appears to be the most effective method of increasing copper excretion but Bearn[11] has pointed out that its usefulness depends on its ability to achieve and maintain a negative copper balance; to do this it must be given more intensively than is conventionally advocated. Moreover, the degree of benefit that can occur depends on the amount of irreversible structural damage to the brain before treatment is started. Bearn divided his patients with H.L.D. into two groups, the BAL-sensitive and the BAL-resistant, the latter group consisted principally of patients who had the more acute forms of the disease. To the more chronic, or BAL-sensitive group, he gave 200 to 300 mg. of BAL twice daily for many months; some of these patients showed a striking and continued improvement. Unfortunately, in some patients severe toxic reactions to BAL may develop such as skin rashes, fever, an exacerbation of the neurologic signs and even hallucinations or coma.

Clearly, there is a need in the treatment of Wilson's disease for a compound that can be given orally on a regular basis or in repeated courses for many years and which is free from toxic side-effects. Such a compound must be easily soluble, so that it is rapidly absorbed from the intestine; it must have one or more stable —SH or other chelating groups and be readily excreted in the urine. Cysteine (CH_2SH $CHNH_2COOH$) does not meet these requirements because the —SH group is rapidly oxidised in the body to the disulphide, cystine, so that it is not available for binding copper. Methionine, which after demethylation can give rise to homocystine ($CH_2SHCH_2CHNH_2$ $COOH$), has been found to be ineffective,[12,8] an observation which has been confirmed in the present study.

It has been shown that patients with liver

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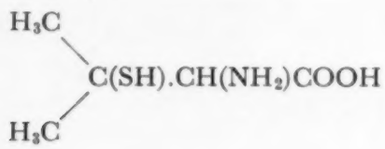
injury who receive parenteral penicillin excrete a degradation product, penicillamine, in the urine.[13] Penicillamine, or β,β–dimethyl cysteine, has the following structural formula:



When isolated from urine this compound was shown to be in the reduced state as it gave a characteristic blue color reaction with ferric chloride which is not given by the disulphide β,β,β′,β′–tetramethyl cystine. Since penicillamine is stable in the reduced form, is extremely soluble and is rapidly excreted by the kidneys, it seemed possible that given orally to patients with Wilson's disease it would be effective in promoting the excretion of copper. The initial experimental results which have already been reported made it clear that further trials were justified.[14]

Penicillamine $HCl.H_2O$ has been given orally in gelatine capsules in doses up to 1.5 gm. daily, the maximum single dose being 500 mg., before meals and without the addition of alkali to neutralize the hydrochloric acid. When given intravenously, a molar amount of bicarbonate was added immediately before administration. Sterility was ensured by Seitz filtration. No immediate toxic side reactions were observed with either the oral or intravenous preparations. In all cases, in the normal subjects as well as in the patients with H.L.D., there was a very marked increase in the urinary excretion of copper. In addition to penicillamine a number of other more readily available non-toxic thiols have also been investigated.

METHODS

Full copper balances have not been carried out but all patients were given a diet of copper content calculated at 800 gamma daily from the tables of McCance and Widdowson.[15] A single day's diet was analyzed and found to contain 700 gamma of copper so that it is probable that on no day did the copper intake exceed 1 mg. Copper was estimated colorimetrically as diethyl dithiocarbamate by a modification of the Earl[16] method in order to obtain twenty-four hour determinations. It was found that a more accurate final reading could be made on a junior Coleman or Unicam spectrophotometer at a wave length of 440 Ä than on a Klett-Summerson colorimeter. Results were reproducible to within 5 per cent by this method. However, in view of the low results for copper excretion obtained with BAL and the high ones observed after penicillamine it was decided to check the Earl method against the more accurate but also the more laborious method of Cartwright et al.[17] The comparative figures are given in Table I. These make it clear that the correspondence between the two methods is sufficient to permit valid conclusions from the results obtained by the Earl method. Moreover a single experiment has been carried out in which 100 microcuries of radioactive copper (Cu^{64}) was given intravenously to a patient with Wilson's disease (Case v) followed four and twenty-four hours later by oral doses of 600 mg. of penicillamine. For twenty-eight hours after the injection of Cu^{64} the rate of copper excretion in the urine was studied both by the Earl method and by estimating the amount of radioactivity present. This showed that the results obtained for copper excretion by the Earl method, both in the resting state and after oral penicillamine, could be accepted without reservation. These results will be published in detail elsewhere. A further investigation into the reason for the low results on BAL days, using the Earl method, showed that the initial amyl alcohol extraction for the removal of alcohol-soluble pigment in the urine also removed at least 10 per cent of the copper.

TABLE I
URINE COPPER

Case	Experiment	Method of Cartwright et al. (1954)	Method of Earl (1954)
Control	Oral penicillamine 0.5 g.	273 μg. (4 hrs.)	220 μg. (4 hrs.)
3	Intravenous penicillamine 225 mg. (free base)	1038 μg. (4 hrs.)	1280 μg. (4 hrs.)
4	B.A.L. 200 mg., intramuscular	910 μg. (24 hrs.)	750 μg. (24 hrs.)
5	B.A.L. 200 mg., intramuscular	801 μg. (24 hrs.)	760 μg. (24 hrs.)
6	B.A.L. 200 mg., intramuscular	670 μg. (24 hrs.)	450 μg. (24 hrs.)
	B.A.L. 400 mg., intramuscular	740 μg. (24 hrs.)	525 μg. (24 hrs.)
	'Versene' 3.0 g., intravenous	1028 μg. (24 hrs.)	950 μg. (24 hrs.)
	Penicillamine 1.5 g., oral	3660 μg. (24 hrs.)	3200 μg. (24 hrs.)

Plasma copper was estimated by the method of Gubler, Ashenbrucker, Cartwright and Wintrobe.[18]

CASE REPORTS

CASE I. (Previously reported by Denny-Brown and Porter,[7] Case II.) This forty-two year old Italian male first complained of tremor of the hands in 1945. Wilson's disease was diagnosed. In 1948 the patient was started on intermittent courses of BAL and there

was marked clinical improvement. In March 1955 ascites developed. The patient temporarily responded to a 200 mg. sodium diet in the hospital but ascites recurred soon after his discharge. One of the patient's four siblings died of Wilson's disease at the age of thirty-seven years. Physical examination in 1955 showed evidence of well-developed hepatic cirrhosis, tremor of the head and arms which was greatly accentuated on movement and Kayser-Fleischer rings. The daily urinary copper excretion was 200 to 300 gamma and paper chromatography showed a moderate aminoaciduria.

CASE II. An eighteen year old boy whose illness started at the age of fourteen with difficulty in speech, in running and in riding a bicycle. Later severe tremor of the head and arms developed in this patient. Wilson's disease was diagnosed and he was started on intermittent courses of BAL. This was followed by improvement in the use of his legs but there was no improvement in his speech. Shortly before his admission for study in August 1955 some personality difficulties developed. Physical examination revealed dysarthria, tremor of the head and arms which was accentuated on movement, a left extensor plantar response and Kayser-Fleischer rings. There was no evidence of liver damage. The daily copper excretion was approximately 400 gamma. Paper chromatography showed a moderate aminoaciduria.

CASE III. A sixteen year old girl whose illness started three years previously with slowness of speech, tremor of the arms and deterioration in her performance at school. The illness progressed until September 1955 when Wilson's disease was diagnosed. By this time the patient was almost inarticulate and was severely disabled by rigidity and early contractures.

Physical examination showed a typical facile grin with drooling at the mouth and a severe cogwheel rigidity with little tremor. Kayser-Fleischer rings were present. Both the liver and spleen were palpable. It was not possible to collect accurate twenty-four hour urine specimens but timed collections showed that the patient excreted between 60 and 100 gamma of copper in a four-hour period. Paper chromatography showed a moderate aminoaciduria.

CASE IV. A nineteen year old girl whose illness had started two years previously with an irregular jerky tremor of the arms. This progressed for eighteen months until the patient was unable to feed or dress herself. After Wilson's disease was diagnosed the patient was started on BAL and there was some improvement. On examination there was tremor of the head and an irregular jerky tremor of the arms of a choreiform type which became wildly exaggerated on movement. Kayser-Fleischer rings were present. There was no clinical evidence of liver damage but the protein flocculation tests were positive. The daily copper excretion was about 300 gamma. Urine aminoacid excretion, as studied by paper chromatography, was at the upper limits of normal.

CASE V. A twenty-six year old man whose presenting sign had been hepatic enlargement noted fifteen years previously. Tremor developed some twelve years later and after Wilson's disease was diagnosed he was started on intermittent BAL which had been continued for the three years before the present study. Physical examination showed tremor of the head and arms which became more severe when attempting fine movements. Kayser-Fleischer rings were present. There was no clinical evidence of liver damage. The urine copper excretion was about 400 gamma daily and the urine amino acid excretion was at the upper limits of normal.

CASE VI. This thirty year old housewife first complained of pain and cramps in her left arm some eighteen months previously. Thereafter irregular jerky movements developed in the patient's left arm and then in her right arm and there was slowness in her speech. The irregular tremor in her right arm progressed more rapidly than that in her left and the patient was soon forced to give up work as a typist. As soon as Wilson's disease was diagnosed the patient was referred for a trial of penicillamine therapy. Examination revealed tremor of the head at rest, choreiform movements of the arms which were greatly increased on movement, Kayser-Fleischer rings and a liver enlarged two fingerbreadths below the costal margin. The daily urine copper excretion was between 300 and 400 gamma. The urine amino acid excretion was slightly in excess of normal. As reference to the results in Table I shows, this patient was exceptionally resistant to the action of BAL in increasing the urinary copper excretion.

RESULTS

Penicillamine HCl was given orally, in three doses of 300 mg. before meals, to two normal subjects and each showed a twentyfold increase in the twenty-four-hour excretion of copper, from 30 to over 600 gamma. (Figure 1.) In all six patients with Wilson's disease there was a similar increase in the urinary excretion of copper following oral administration of penicillamine. These results are shown in detail in Figures 2 to 7 and in summary in Table II. In Cases I, II, IV, V and VI it was possible to make accurate twenty-four-hour urine collections; on the days on which they received 900 mg. of penicillamine HCl, in Cases I and V the patients excreted between 1,000 and 2,000 gamma of copper, in Cases II and VI over 2,000 gamma and in Case IV over 4,000 gamma of cop-

per. As it was not possible to make accurate twenty-four-hour urine collections in case III, factors influencing the copper excretion of this patient were studied over four-hour collection periods from 9 a.m. to 1 p.m. each day although on six occasions consecutive collections were made from 9 a.m. to 1 p.m. and from 1 p.m. to 5 p.m. (periods 3 and 4; 8 and 9; 10 and 11; 12 and 13; 14 and 15 and 18 and 19). After an oral dose of 500 mg. of penicillamine HCl this patient excreted over 2,000 gamma of copper in eight hours, and over 1,000 gamma in four hours after an intravenous dose of 225 mg. of penicillamine free base. (Figure 4.)

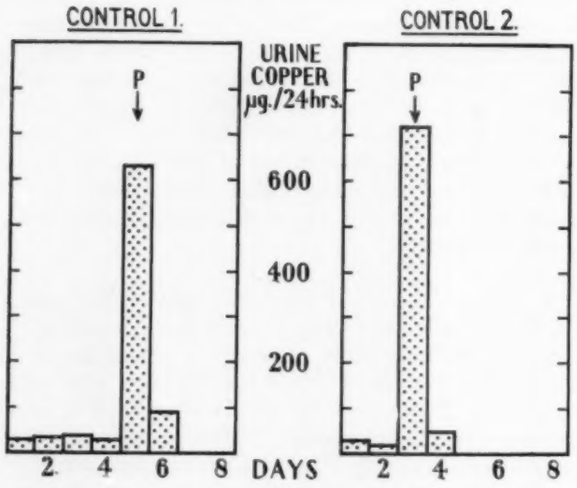


FIG. 1. P = oral penicillamine HCl 300 mg. three times a day.

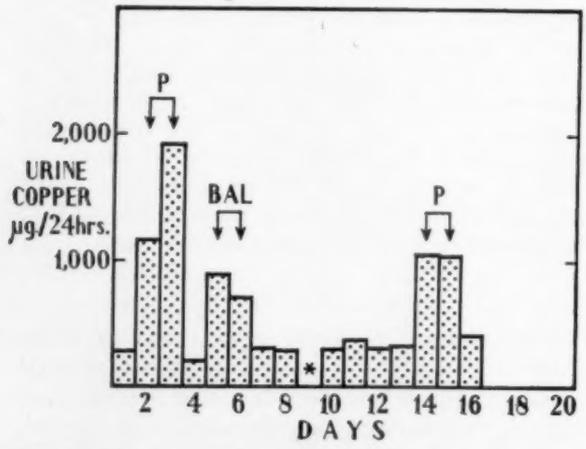


FIG. 2. Case I. Forty-two year old man. P = oral penicillamine HCl 300 mg. three times a day; BAL = 200 mg. BAL intramuscularly daily; * = Lost.

It can be seen from the diagrams that when penicillamine was given in three doses of 300 mg. in twenty-four hours the increase in copper excretion was continued into the next day. By comparison the results obtained after the administration of 200 mg. of intramuscular BAL were surprisingly small; only in Case II did the patient show a larger response to this than to penicillamine while in Case VI the patient was almost completely resistant to the 'de-coppering' action of BAL. Versene was given to a patient only once (Case VI) and like penicillamine it carried on its activity into the following twenty-four hours.

TABLE II
URINE COPPER, µg./24 HOURS

Case	Average Resting Excretion	Maximum Excretion after Intramuscular B.A.L.	Dose	Maximum Excretion after Oral Penicillamine HCl	Dose
Control 1	31	....	.....	630	900 mg.
Control 2	23	....	.....	720	900 mg.
1	285	890	200 mg.	1910	900 mg.
2	430	2510	200 mg.	2320	900 mg.
4	251	750	200 mg.	4800	900 mg.
5	361	760	200 mg.	1770	900 mg.
6	369	525	400 mg.	3200	1.5 g.
4 (4 hr. periods)	82	320	150 mg.	1505	500 mg.

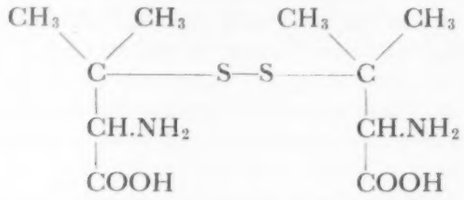
All results in this table were determined by Earl's[18] method.

In Cases V and VI determinations of the urinary copper were not made daily throughout the patient's stay in the hospital but only sufficiently often to demonstrate the general trend of copper excretion throughout the study period. It is calculated that during fifteen days of continuous therapy in Case VI the patient received 13 gm. penicillamine HCl orally and excreted 30,000 gamma of copper while on a diet containing approximately 15,000 gamma of copper. In other words, she was in a negative copper balance of 15 mg. during the study period.

A number of other sulphur-containing compounds that have been investigated showed no activity in promoting copper excretion.

(1) Methionine, 6.0 gm. daily orally. This was found to be inactive. It was given in Case I on days 9 and 10. (Fig. 2.)

(2) β,β,β′,β′-Tetramethyl cystine.



Three doses of 300 mg. were given in Case II on day 12 (Fig. 3) without affecting the urine copper excretion. Dimethyl cysteine may slowly oxidise to tetramethyl cystine in air and this may lead to an apparent failure of therapy. The two compounds can easily be distinguished since tetramethyl cystine does not give the characteristic blue color reaction with ferric chloride given by dimethyl cysteine.

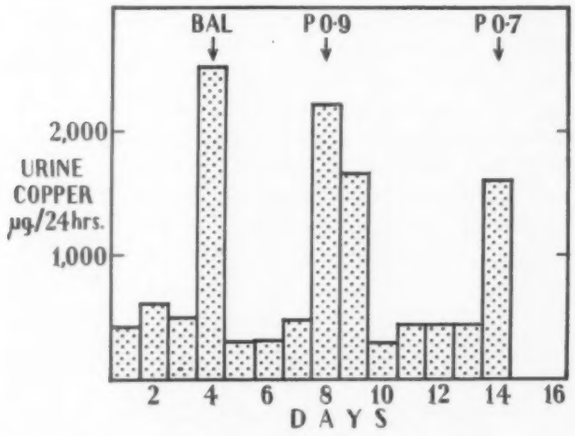


FIG. 3. Case II. Eighteen year old man. BAL = 200 mg. BAL intramuscularly; P 0.9 = oral penicillamine HCl 900 mg.; P 0.7 = oral penicillamine HCl 700 mg.

(3) Cysteine was given in doses of 500 mg., 1.0 gm. and 2.0 gm. daily. There was no significant response. It was given in Case III (Fig. 4) in periods 6 and 17 and in Case IV (Fig. 5) on day 6.

(4) Cystamine. $S—CH_2—CH_2—NH_2$ / $S—CH_2—CH_2—NH_2$

375 mg. of this (sulphur content equivalent to 1.0 gm. penicillamine HCl) was given in Case III. It has been claimed[19] that this compound is reduced in the body to the thiol cystamine, $HS—CH_2—CH_2—NH_2$, which is itself too unstable for oral administration. The single trial carried out in Case III, period 12 (Fig. 4) showed no activity in promoting copper excretion.

(5) Penicillin was given orally in a dose of 2,000,000 units (1,250 mg. penicillin). This compound can break down in the body to give penicillamine.[18] The theoretical yield from penicillin is 40 per cent but this is not achieved even in vitro. Two million units (1,250 mg.) of penicillin would not therefore yield the theoretical maximum of 520 mg. of penicillamine; in fact probably only a small percentage is broken down in the body. The trial was made in Case III (Fig. 4) in period 7; there was only a small increase in the urine copper excretion of doubtful significance.

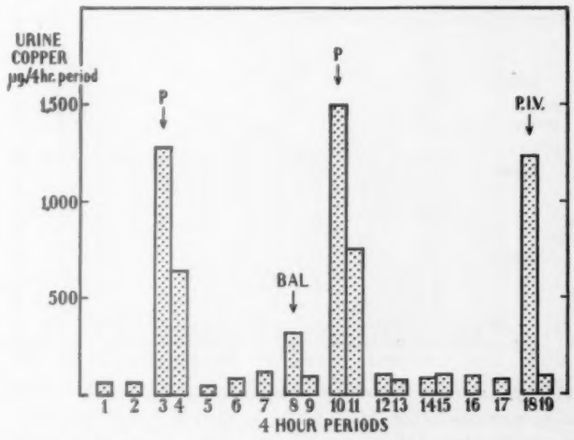
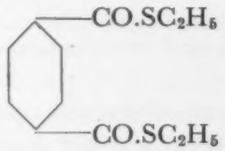


FIG. 4. Case III. Sixteen year old girl; BAL = 150 mg. intramuscularly BAL; P = 500 mg. penicillamine HCl—oral; P.I.V. = 225 mg. penicillamine—free base —intravenously.

(6) Thiourea. CS(NH_2)(NH_2)

1.0 gm of this compound was given in Case IV on day 16 and in Case V on day 10. (Figs. 5 and 6.) In neither instance was there an increase in the urine copper excretion.

(7) Diethyl dithiol terephthalic acid.



This was given in Case IV on days 18 and 19. It did not increase the urine copper excretion when given in doses of 1.0 gm. daily. In the body this compound breaks down to form ethyl mercaptan, C_2H_5SH. However it is extremely insoluble and probably only a small percentage

is absorbed. Ethylmercaptan, which has a highly offensive odor, could be smelled in the patient's breath for eighteen hours after the last dose. There was also a faint smell of mercaptan in the urine.

(8) Finally, in view of the claim[5] that d,l-alanine in large doses increases copper excretion, 12 gm. was given as a single dose in Case III in period 14 without noticeably altering the urine copper excretion. There was however an excess of alanine in the urine measured chromatographically.

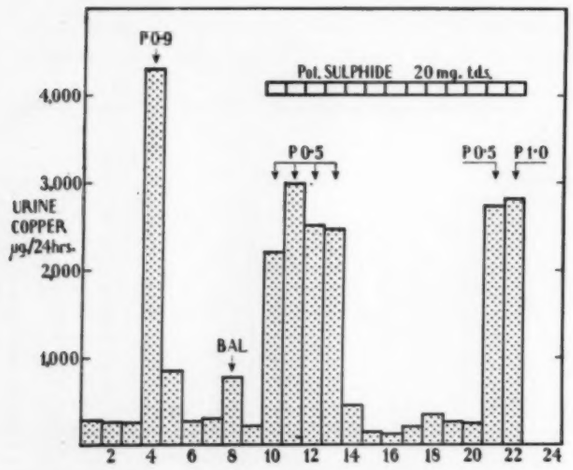


FIG. 5. Case IV. Nineteen year old woman. P 0.5 = 250 mg. penicillamine HCl twice a day; P 0.9 = 300 mg. penicillamine HCl t.d.s.; P 1.0 = 0.5 g. penicillamine HCl twice a day; BAL = 200 mg. BAL intramuscularly.

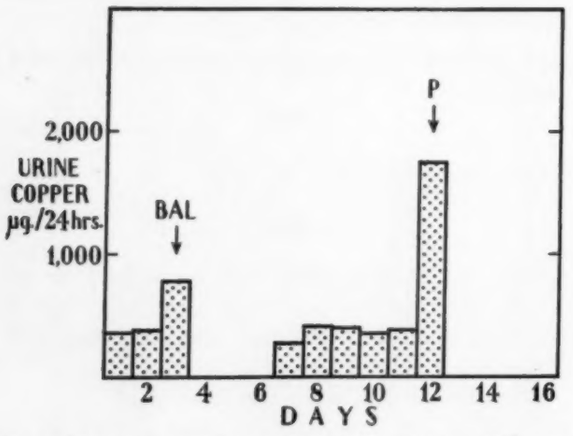


FIG. 6. Case V. Twenty-six year old man. BAL = 200 mg. BAL intramuscularly; P = 900 mg. penicillamine HCl.

In Cases IV and VI the effect of penicillamine on the plasma copper concentration was also studied. One hour after the oral administration of 0.5 gm. of penicillamine HCl the plasma copper rose from a resting level of 59 gamma per 100 ml. to 81 gamma per 100 ml. in Case IV and from 61 gamma to 85 gamma per 100 ml. in Case VI. Finally, three days after the completion of a two weeks course of penicillamine therapy the plasma copper concentration fell, in Case VI to 44 gamma per 100 ml., thirty per cent below the initial fasting level.

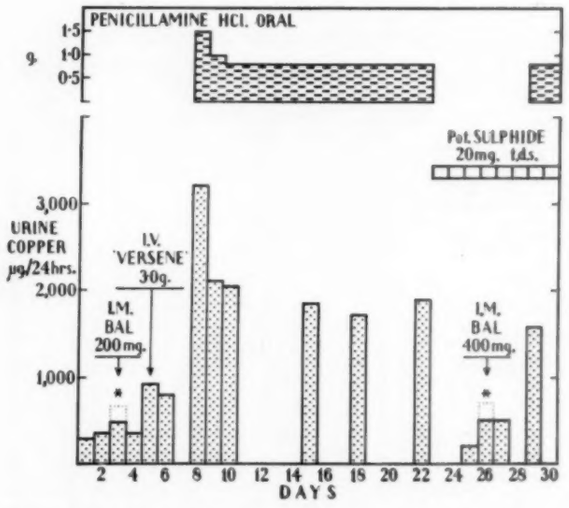


FIG. 7. Case VI. Thirty year old woman. Dotted line shows result obtained by method of Cartwright et al. (1954).

COMMENTS

Evidence for the action of BAL in normal subjects is contradictory. Cumings[20] found no increase in the urine copper of three normal subjects after BAL therapy and Cartwright et al.[9] also state that BAL is inactive in promoting copper excretion in normal subjects although they do not give their evidence. Mandlebrote and Thompson[6] noted a small increase, as did Matthews, Milne and Bell.[8] After intravenous BAL, McCance and Widdowson[21] noted a large increase in the urine copper of normal subjects and a very large increase in the urine zinc, but no change in the iron content. In the present study penicillamine, when given orally to two normal subjects in three doses of 300 mg. in twenty-four hours, resulted in a twentyfold increase in the urinary copper, a finding more in keeping with the results of McCance and Widdowson than those of other workers.

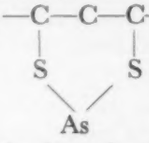
In Wilson's disease it is now well established that BAL causes a significant cupruresis but the

actual amount of copper excreted varies greatly from case to case, figures varying from no response in some patients to 4,000 gamma daily. A similar increase is found after intravenous versene but not after oral versene. The best results have been obtained by a combination of intravenous versene and intramuscular BAL, but none of these forms of treatment can be given to the patient continuously in his home.

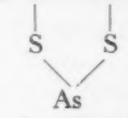
It seems clear from the results reported in this paper that penicillamine, when given orally, is a highly effective agent for the removal of copper from patients with H.L.D. If, as seems probable, removal of the excess copper from such patients results in clinical improvement, it is to be expected that prolonged administration of penicillamine will be a valuable addition to the treatment of this condition. When considering any form of oral medication for Wilson's disease the criticism must be met that the increased excretion of copper in the urine is more apparent than real. A compound with a strong affinity for copper might become fully saturated in the intestine and actually carry more copper into the body than it subsequently removes in the urine. In these studies the amount of copper excreted after single or multiple doses of penicillamine commonly exceeded the total daily amount of copper in the diet by three- or fourfold, but even stronger evidence for the activity of penicillamine was obtained. Intravenous penicillamine, 225 mg. of free base, was given in Case III (study period 18), after which 1,200 gamma of copper was excreted in the urine in four hours instead of the expected 100 gamma.

Whether penicillamine will prove to be of equal value in the treatment of other heavy metal intoxications is a matter of conjecture but these results would appear to justify its trial in the treatment of poisoning by the divalent metals, gold and mercury.

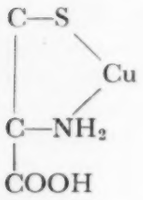
The activity of penicillamine, a monothiol, in the removal of copper requires comment as it has been shown that the activity of BAL is due to its dithiol groupings.[22] BAL, however, falls far short of the theoretical maximum in removing copper from patients with H.L.D. If each molecule of BAL (molecular weight 124) removed one atom of copper (atomic weight 63) a 200 mg. dose of BAL should combine with almost 100 mg. of copper whereas in fact it will only increase the copper excretion by about 1 mg., an efficiency of only 1 per cent. However, McCance and Widdowson showed that other metals were also being removed from the body at the same time. It may be that a dynamic equilibrium is reached by the tissue copper between BAL and the naturally occurring sulphydryl groups; this can also be achieved by a monothiol such as penicillamine. In arsenic toxicity the position is much better understood. It has been shown experimentally that the monosubstituted organic arsenicals, such as lewisite, block the pyruvate oxidase system by combining with the thiol groups of lipoic acid (6,8 dithioloctanoic acid) forming a six membered ring —C—C—C—C— which is only



slightly less stable than the five membered ring formed with BAL



This inhibition of pyruvate oxidase is followed by accumulation of pyruvate in the blood. This work has been fully reviewed by Peters.[23] Metallic poisoning of a dithiol enzyme system could not be reversed by a monothiol such as penicillamine. The disubstituted arsenicals on the other hand act at a different point and the inhibition can be reversed equally well by monothiol compounds such as monothiol ethylene glycol or glutathione, at least in vitro. The enzyme system blocked by copper is not known but, as the principal accumulation of copper is in those organs with most Krebs cycle activity, it is probable that some enzyme necessary for the proper functioning of this system is inhibited. The plasma citrate was estimated in two cases in the present series and was normal, which suggests that the enzyme necessary for the further metabolism of this particular acid is not involved. However, as it is not the dithiol lipoic acid that is blocked by copper there is no reason why a monothiol such as penicillamine should not prove active in removing copper from patients with Wilson's disease. The bond between copper and penicillamine might take one of three forms, (1) a single atom of copper being bound to a single sulphydryl group, C—S—Cu^+; or (2) an atom of copper might be linked between the sulphydryl groups of two penicillamine molecules, C—S—Cu—S—C; or (3) a ring compound might be formed by one atom of copper linking with both the —SH and the —NH_2 groups of a single penicillamine molecule,



The failure of ethylmercaptan to promote the excretion of copper suggests that the —SH group alone may not be enough and that the ring structure is in fact the active one in penicillamine.

In these short term experiments no toxic reactions were noted from penicillamine in the doses used. It is however possible that when used for long term maintenance therapy dimethyl cysteine might enter the same metabolic pathways as cysteine and cause a block. Occurring in the liver a metabolic block might lead to a conditioned cysteine deficiency and hepatic necrosis, in the skin it might cause alopecia as does selenium cystine.[24] These points can be resolved only by a long term study. Such complications have not been observed under laboratory conditions. When added to a choline-free diet in a concentration of 0.35 per cent L-penicillamine causes immediate loss of weight and eventually death in young albino rats.[25] Such an experiment is highly unphysiological both as regards the diet and the dose of penicillamine, equivalent to 10 gm. in a 70 Kg. man, far higher than is needed in the treatment of Wilson's disease. Moreover, if penicillamine is obtained from penicillin it is as the 'D' isomer, which these authors showed to be non-toxic and which Taylor and Gordon[26] have shown to be a growth-promoting factor for chicks and pigs. Wilson and du Vigneaud[25] also found that the toxic action of L-penicillamine could be completely reversed by the addition to the diet of ethanolamine or one of its methyl derivatives but not, surprisingly enough, by cysteine or methionine, suggesting that any action it may have as an antimetabolite is by interfering with transmethylation rather than sulphur metabolism. The penicillamine used in these experiments has been tested for acute toxicity on mice and rats and was tolerated in doses far outside the therapeutic range.* There does, in fact, appear to be no serious risk attached to the use of penicillamine for the maintenance therapy of Wilson's disease but as a precautionary measure the patients should be weighed regularly and supplements of ethanolamine or choline added to the diet.

SUMMARY

Of the compounds currently used in the treatment of Wilson's disease BAL appears to be the most generally useful. However, it has a disadvantage in that toxic reactions eventually develop in many patients.

A new form of oral treatment with dimethyl cysteine (penicillamine) is described. Given in doses varying from 0.5 to 1.5 gm. daily to six patients with Wilson's disease, it provoked a very large increase in the urine excretion of copper; in five patients it proved more active than BAL in this respect.

No toxic reactions were observed in any patient in these short term trials. Possible toxic reactions and precautions to be taken in the long term use of this compound are considered.

It is pointed out that, on theoretic grounds, dimethyl cysteine may well be of use in the treatment of heavy metal poisoning with gold or mercury.

ACKNOWLEDGMENTS

Sources of Penicillamine. dl-Penicillamine for trial in Cases I and II was given by Dr. Augustus Gibson of Merck & Co., Inc. of Rahway, N. J. and Professor John Sheehan of The Massachusetts Institute of Technology. That used in Cases III, IV and V was purchased from Mann Fine Chemicals of New York, and in Case VI d-penicillamine was a gift from the Distillers Company (Biochemicals) Ltd. of Speke, Liverpool.

I am most grateful to those physicians whose cooperation made this study possible by allowing me to carry out trials on their patients; Cases I and II, Dr. D. Denny-Brown, Case III, Dr. Michael Ashby; Cases IV and VI, Dr. Dennis Brinton; and Case V, Dr. J. N. Cumings. I am also indebted to Sir Rudolph Peters for supplies of cystamine, to Drs. Davies and Driver of Imperial Chemical (Pharmaceuticals) Ltd. of Blackley, Manchester for their gift of diethyl dithiol terephthalic acid and to Dr. Augustus Gibson of Merck for $\beta\beta\beta'\beta'$-tetramethylcystine. Finally, I wish to thank Dr. C. S. Davidson

* The penicillamine given by Merck was tested for acute toxicity by Mr. Samuel Kuna. It had no toxic effects when given to mice in doses of 500 mg./Kg. Penicillamine given by the Distillers Company was tolerated by mice in doses of 100 mg. in each of five 20 gm. mice (5 gm./Kg.) and in a second group tested all nine mice survived a similar dose.

of the Thorndike Memorial Laboratory without whose help this work could never have been started.

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Renal Vein Thrombosis and the Nephrotic Syndrome*

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THE nephrotic syndrome, which appears with severe pain and fullness in the loins, hematuria, fever and leukocytosis, may be due to renal vein thrombosis—a clinical association which has been rarely reported. During a study of serial renal biopsy specimens from patients with the nephrotic syndrome,[33] we observed two patients whose illness followed renal vein thrombosis.[49] In one patient the disease was diagnosed during life; this patient was successfully treated and has recovered. The purpose of this paper is to describe in detail the clinical features of this case—which we believe to be the first of its kind diagnosed and treated successfully—to review the clinical and pathologic features of the published cases; to discuss the relevant experimental work; and to delineate the clinical syndrome.

HISTORICAL REVIEW

Clinical. Richard Bright was the father of scientific observation in diseases of the kidney. Less well known, at least in the English speaking world, is his French contemporary P. Rayer who in 1827 first described lupus erythematosus in his "Traité Théorique et Pratique des Maladies de la Peau,"[50] and who in 1840 wrote a classic text, "Traité des Maladies des Reins."[51] He made observations on the clinical features, urinary findings and pathology in a wide variety of diseases affecting the kidney. This eminent French observer described seven cases of renal vein thrombosis in which two patients had the nephrotic syndrome. One of these patients was a fifty-seven year old laborer who suffered from tuberculosis and in whom massive edema and extreme proteinuria developed five months before he died. At the autopsy both kidneys were increased in weight and the renal veins were filled with old thrombi. The kidneys from the second patient are shown in Figure 1.

Six years later, in a communication to the Société Anatomique de Paris, Delaruelle[14] described a case in a twenty-six year old woman. He observed many features which occurred in our patients: his patient had recurrent chest pain with bilateral pleural rub and abdominal pain, which came on gradually, was persistent and was not relieved by laudanum. Swelling of the feet occurred at the same time as the abdominal pain and an abundant white precipitate appeared when the urine was tested with heat and nitric acid. Edema of the legs increased and the face became swollen. At the autopsy the kidneys were enlarged to approximately twice their normal size. The inferior vena cava was blocked by a firm fibrous thrombus which extended from above the junction of the iliac veins to above the renal veins, thrombosis extended up into both renal veins and completely blocked the left vein.

In 1854 Vidal[65] presented another case of renal vein thrombosis to the Société Anatomique de Paris—a twelve year old boy with diarrhea, generalized edema, persistent pain in the region of the kidneys and gross proteinuria. At the autopsy the renal veins were inflamed and filled with clots from which pus was expressed.

Following this, no cases of renal vein thrombosis were reported until 1922, when Neu[43]

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described his observations of a young woman who died in uremia. Thrombosis of both renal veins was found postmortem and there were amyloid deposits in the spleen and kidneys. In 1937 Heilmeyer and Lippross[26] reported a case and stressed the importance of albuminuria and hematuria in the diagnosis. They emphasized that pain in the loin with enlargement of the kidney were important features of the syndrome.

The first case described in the English speaking literature was reported in detail in 1939 by Derow et al.[15] In the past fifteen years several cases of renal vein thrombosis with the nephrotic syndrome have been mentioned briefly[3,5,16,20] and six cases have been reported on completely.[6,23,37,39,58,64] The patient reported on by Vallery-Radot[64] was acutely ill with fever, leukocytosis and pain and tenderness in the loin. A mass was palpated in the abdomen and a diagnosis of perinephric abscess was made. At the operation the kidney was as large and as purple as an eggplant. The patient died a few days later and thrombosis of both renal veins was seen at the autopsy.

One other case of a patient with occlusion of both renal veins is of interest in relation to the prognosis in this disease—that reported by Shattock in 1913.[57] This was the case of Dr. W. Rivers Pollock who in 1884 won the Oxford and Cambridge 120 yard hurdle race for Cambridge University in what was then the record time of sixteen seconds. During the entire race he held his breath. Immediately after the race Dr. Pollock complained of severe pain in the lumbar spinal region. "He was put to bed, where he remained for six months. Edema of the legs, and to a lesser extent, of the abdomen and scrotum, supervened at once, and persisted for the period mentioned. Whilst in bed, the superficial veins began, within a few days, to dilate, and their enlargement slowly progressed. . . . Albuminuria appeared directly after the event, and persisted throughout life." Death from tonsillitis and septicemia occurred twenty-five years later.

At the autopsy the inferior vena cava, except for its highest part, was " . . . converted into a flat, impervious ribbon, most contracted and thinnest for a distance of 6.5 cm. opposite to and below the renal veins. The common iliac veins and the parts of the external and internal preserved are likewise flattened and obliterated. . . . The tributaries and trunk of the left renal vein are pervious, although as tested with the probe, the entrance of the latter into the cava is closed; the same is true of the trunk of the right renal vein."

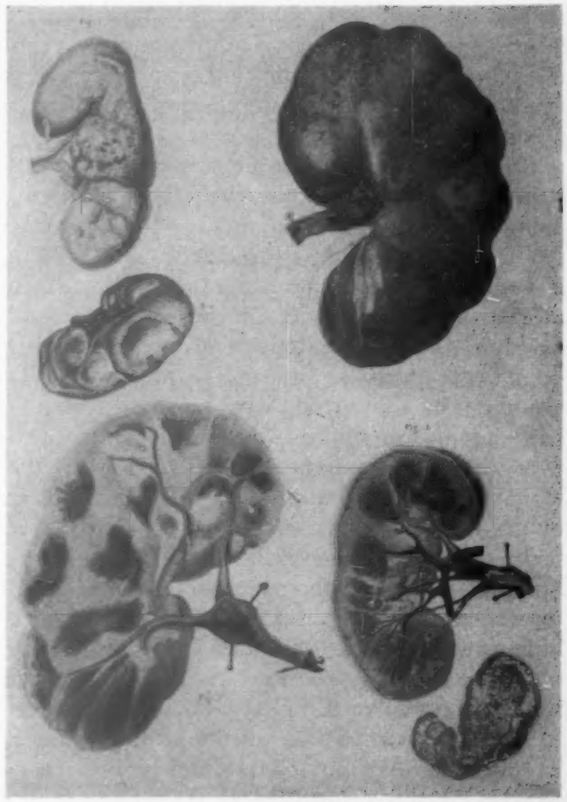


FIG. 1. Plate VII in Rayer's Atlas. In the upper right hand corner note "the left kidney of a young girl who died with generalized edema and albuminous urine. The kidney is very lobulated. The cortex is very swollen with a white-yellow hue resembling apricot yellow but it was not severely anemic. 'Les polygones vasculaires' of the cortex are still visible at several points. The renal vein is filled by a solid fibrinous clot which extends into its main divisions. The fibrous capsule of the kidney is thickened over the lower pole." In the lower left corner note "the cut section of the right kidney of the same patient. The apricot yellow hue of the cortex is very marked. The right renal vein, like that on the left, is filled with a fibrous adherent mass which extends into its main branches. The walls of these veins are thickened."

Shattock puts forward the hypothesis "that in consequence of the extreme distension of the inferior vena cava occasioned by the holding of the breath throughout the race, a localized rupture of the intima, or of this and the media, took place, which was followed by the forcible extravasation of blood into the walls of the vein whilst the exertion was still in progress; that the lesion, in short, in the initial stage, was the counterpart of a dissecting aneurysm of the aorta." The return of blood from the kidneys must have taken place through the veins of the capsule and

thence by way of the lumbar through the enlarged azygos vessels. Unfortunately, postmortem changes in the kidneys were very marked and no exact description of the kidneys was available.

Experimental. For over a century experiments have been conducted on the effects of compression of the renal veins. In 1843 George Robinson,[53] a friend of the celebrated William Bowman, reported a series of experiments to the Royal Medical and Chirurgical Society of London. He was attempting to determine " . . . the precise cause of the appearance of albumen in the urine." In his first series of experiments on rabbits Mr. Robinson applied ligatures tightly around one renal vein; in the second series he attempted to effect incomplete or gradual obstruction of the vein. In the first series the animals were killed within an hour of ligation; in the second they were killed at intervals of from thirty minutes to four and one-half days after the operation. Albuminous or bloody urine was produced in all cases and the weight of the affected kidney was approximately twice the weight of the normal kidney. Similar experiments were carried out later by Frerichs,[21] Meyer,[35] Munk[42] and Erythropel.[18] Their observations also extended over a period of four days at the most.

In 1876 Buchwald and Litten[11] made serial studies of the development of the histologic changes in the kidneys of animals after obstructing the renal venous circulation. Their observations extended over periods up to eight weeks. They observed that soon after ligation the kidney became dark red and swollen. Edema developed and bleeding occurred under the capsule. By twelve hours fat droplets appeared in the renal epithelium, an observation which had been made previously by Munk.[42] In the next twenty-four to thirty-six hours the kidney became bluish red in color, was mottled with yellowish fatty areas in the cortex and hemorrhage was visible microscopically. These changes increased until by the sixth day the size and weight of the affected kidney began to decrease. By the ninth to thirteenth day the affected kidney was smaller than the normal. Buchwald and Litten emphasized that the glomeruli were apparently unchanged despite intense degenerative changes in the tubules, as a result of which the glomeruli appeared closer together than normal. Much detritus clogged the tubules. Inflammatory changes were absent. After forty days this crowding together of the glomeruli was very obvious. In two of the animals excellent collateral circulation developed from the kidney capsule to the inferior vena cava and the suprarenal, lumbar and diaphragmatic veins.

Alessandri,[2] Isobe[29] and Harrington,[25] among others, reported similar findings. Pawlicki[46] found that when ligation of the renal vein resulted in irremediable damage to the kidney, a collateral circulation did not develop. On the other hand if a collateral circulation developed, the organ survived and function was preserved. Jungano[31] suggested that in man, when the renal vein was slowly occluded by a thrombus, a collateral circulation developed more readily than in the experimental animal in which the vein was occluded instantaneously by ligature.

In 1913 Rowntree, Fitz and Geraghty[54] used an obstructing band to produce chronic congestion in the kidneys of dogs. They observed that " . . . when gradual progressive obstruction to the renal vein occurred, the development of a collateral circulation is of great importance in maintaining the functional capacity of the kidney since an efficient renal function may be encountered when the venous return from the kidney is entirely collateral. On the other hand, ligation of collateral vessels, simultaneously with a moderate degree of obstruction to the renal vein, usually results in renal inefficiency and death." As the degree of experimental chronic congestion of the kidney increased, Rowntree et al. observed that the amount of urine decreased; the urine contained increasing amounts of albumin, casts and red blood cells and the functional capacity of the kidney decreased.

In 1932 Orofino[45] reported that, after experimental ligation of the renal vein, function (as measured by the excretion of water, urea, chloride and phenolsulfonphthalein) diminished. He noted that renal function in one dog was poor three days after the operation but returned to normal at fifteen days. On reopening the abdomen he found that the occluding ligature had slipped.

Braun-Menendez[9,10] noted a rise of more than 20 mm. Hg in the arterial pressure in four of eight dogs after the renal veins had been partially tied. This occurred in the second postoperative week and lasted as long as two months. This effect of ligation of the renal vein was not produced when the renal veins were divided. Friedberg[22] observed that in dogs partial venous occlusion sometimes led to transitory mild

hypertension which disappeared as an extensive capsular collateral vascular network developed. However, in one dog the hypertension persisted for over two years. When the newly formed collateral veins were occluded by reoperation, a more severe and long-lasting hypertension was produced in some cases.

In 1949 Blake and his associates[8] raised the pressure in the left renal vein for twenty to thirty minutes by means of a clamp. They observed that even a moderate rise in pressure, to 160 mm. saline solution (normal 80 to 120 mm. saline solution), caused a marked decrease of water and sodium excretion but the glomerular filtration rate and renal plasma flow remained constant. The ratio C_{Na}/C_{Cr} was decreased. However, when the venous pressure was raised to 550 mm. saline solution, the glomerular filtration rate and renal plasma flow decreased. The increased reabsorption of water and sodium occurred only in the kidney in which the venous pressure was raised, indicating that this was due to local rather than to distant hormonal or neurogenic factors. Selkurt[56] noted that when the renal venous pressure was raised immediately to 300 mm. saline solution the $C/_{Cr}$ and $C/_{PAH}$ on the average decreased by 15 per cent. There was no change in the filtration fraction. Jeanneret[30] reported a similar fall in the clearance of creatinine but the decrease in PAH clearance was 31 per cent and the filtration fraction was consequently elevated. The clearance of sodium was decreased by 29 per cent. Hwang et al.[28] noted that after constricting the inferior vena cava of dogs above the renal veins, the renal venous pressure rose to between 235 and 365 mm. saline solution. An initial proportional reduction of renal plasma flow and glomerular filtration rate resulted and the sodium excretion was reduced in three of four dogs. By the seventh postoperative day, however, the sodium excretion had reached the preoperative levels.

In man, Farber, Becker and Eichna,[19] by inflating a balloon in the inferior vena cava, raised the venous pressure above the renal veins. The pressure was kept for thirty minutes at between 100 and 250 mm. saline solution, and during this time they observed decreased urinary excretion of sodium and chloride and, less constantly, of water. Renal plasma flow and glomerular filtration rate usually decreased initially by 15 to 25 per cent. As the venous congestion was maintained, these functions improved and at the end of thirty minutes were returning toward control values while the water and electrolyte excretions remained at their low levels. Following the release of inferior vena caval congestion, water and electrolyte excretions, renal plasma flow and glomerular filtration rate returned to control levels; the renal hemodynamic functions promptly, the urinary excretions, within thirty minutes. The levels to which the venous pressure were raised were comparable to those encountered in congestive cardiac failure and were much below those encountered in experimental partial ligation of the renal vein.

Numerous experiments in this field have been made for over one hundred years. In all a single effect has been studied and, frequently, for brief periods only. Edema and the biochemical changes of the nephrotic syndrome have not been reported.

CASE REPORT

Pleuritic pain suddenly developed in a healthy thirty-five year old cement finisher. A few weeks later, pain and tenderness in the left loin were noted. Within a few days edema of the face, hands and legs appeared and protein was found in the urine. The biochemical changes of the nephrotic syndrome were found and subacute glomerulonephritis was diagnosed. Following this the patient had recurrent chest pains and became severely ill. Three months after the onset, very severe persistent pain suddenly occurred in the right flank, radiated to the right testicle, and was accompanied by tenderness, fullness and rapid enlargement of the right kidney. The patient was feverish and critically ill. High leukocytosis was present. A diagnosis of nephrotic syndrome with renal vein thrombosis was made but perinephric abscess was also considered. Shortly thereafter, a thrombosis of the right common iliac vein developed, which spread to involve the left common iliac. A biopsy specimen of the kidney revealed gross interstitial edema and hemolytic enterococci were grown from the kidney tissue. Treatment with heparin and antibiotics brought about a dramatic improvement in the patient's condition but the right kidney became atrophic and was removed. Despite residual edema of the legs and continued gross proteinuria, the patient returned to full time work.

B. B. (R. & E. No. 422045), a thirty-five year old white male cement finisher, was admitted for investigation to the University of Illinois Hospitals on October 15, 1954. Until July, 1954 the patient had enjoyed good health. Early in July he experienced a sudden severe pain in the left scapular region. This pain was more severe when the patient breathed and he soon became acutely breathless. During the next several hours the shortness of breath gradually subsided. His physician made a diagnosis of pneumonia and instituted antibiotic therapy. The symptoms subsided within a week. A few days later a moderately severe ache in the patient's left flank and hypogastrium developed. This

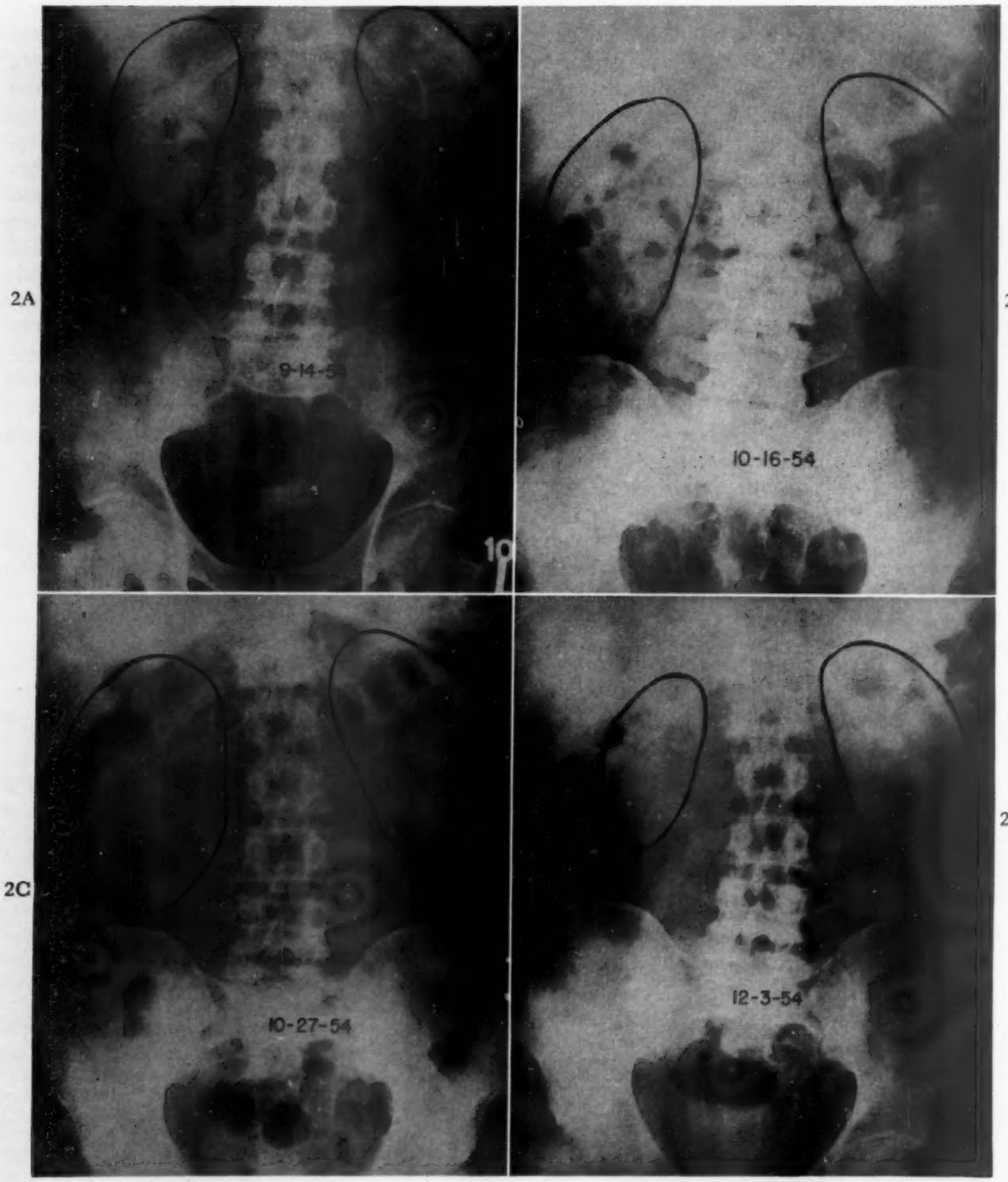
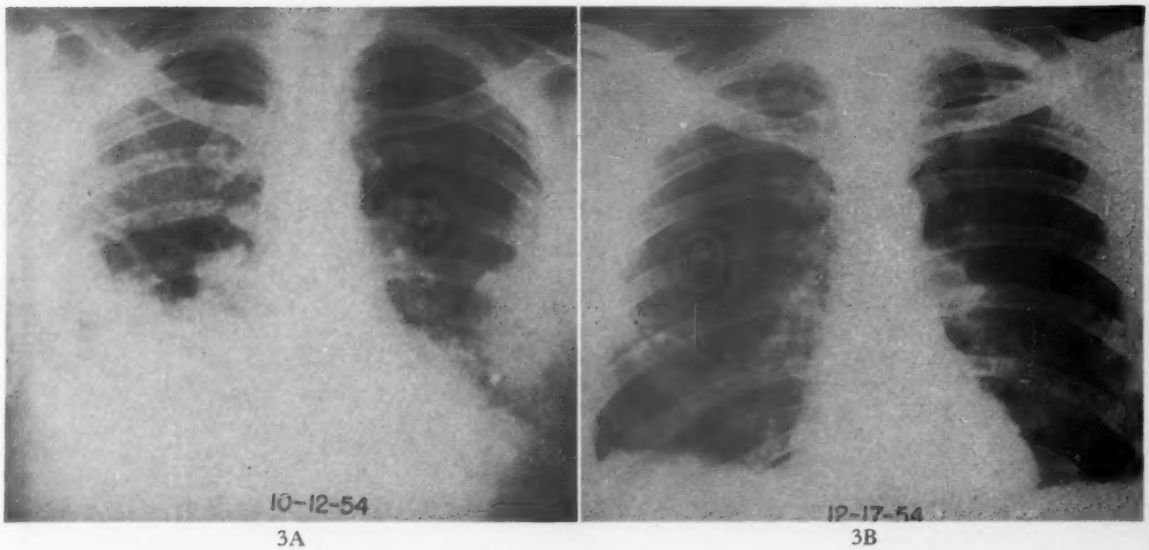


FIG. 2. Serial x-ray studies of the kidneys in patient B. B. before and after thrombosis of the right renal vein. A, intravenous pyelogram, note moderate enlargement of left kidney, normal-sized right kidney and excretion of dye good from both sides. B, beginning enlargement of right kidney. C, huge right kidney. D, note right kidney has shrunk and is smaller than normal (A).

began as a soreness and increased to a constant, severe, dull ache which interfered with his sleep. When severe, it radiated down into the left testicle. It lasted for fourteen days in all. A few days after its onset the patient noticed swelling of the hands and periorbital tissues and of the legs up to the knees. He had mild diarrhea for a few days. The patient was admitted to another hospital where examination confirmed the distribution of edema. Marked tenderness was noted in the left loin. The blood pressure was 170/100 mm.



3A 3B

FIG. 3A and B. Serial x-ray studies of the chest in patient showing the appearance and clearing of multiple pulmonary infarctions.

Hg and the retinal arterioles were attenuated. The liver, spleen and kidneys were not palpable and no other abnormality was found on physical examination.

The hemoglobin was 14 gm. per 100 ml.; the leukocyte count was 8,800/cu. mm. with a normal differential count. The serum nonprotein nitrogen was 20 mg. per cent, the serum protein was 5.1 gm. per 100 ml. and the serum cholesterol was 360 mg. per 100 ml. The urine had a specific gravity of 1.010, contained protein (0.3 gm./L.), red blood cells and a few granular casts. An intravenous pyelogram showed good excretion; the left kidney was considerably larger than the normal-sized right kidney. (Fig. 2A.) Infiltration in the left lower lung field was seen in the x-ray of the chest. These findings persisted until the patient's discharge from the hospital on September 17. A diagnosis of subacute glomerulonephritis was made by his physician.

Third Month of Illness. A few days later the patient had another attack of pleuritic pain and was readmitted to the hospital on September 28. His temperature was 99.8°F. and the blood pressure was 140/85 mm. Hg. There was dullness and the breath sounds were absent at the left lung base. Tenderness over the left upper quadrant of the abdomen was noted. This disappeared within a week. There was no edema.

The patient's clinical condition deteriorated steadily and the temperature rose to 101°F. On October 5 pleuritic pain developed in the right side of the patient's chest. There was a leukocytosis of 18,700/mm.^{3} (86 per cent neutrophils). The urine specific gravity was 1.010; it contained 500 mg. of protein per L. and a few white blood cells were seen in the sediment. The serum non-protein nitrogen was 41 mg. per cent; numerous laboratory studies which were done were of no help. Administration of antibiotics failed to influence the course of his illness. Roentgenograms of the chest showed progressive infiltration of the lung fields and bilateral pleural reaction. (Fig. 3A.) When the patient began having recurrent small hemoptyses, he was transferred to the University of Illinois Hospitals.

The past history and family history were not helpful; there was no history of previous renal disease.

On admission to the hospital the patient looked chronically ill, sallow, tired, flabby, and had lost weight. He was slightly short of breath in bed. The temperature was 101°F., pulse 100 per minute, respiration 36 per minute, and blood pressure 160/100 mm. Hg. The heart was normal in size; there was a systolic gallop rhythm but no murmurs were heard. Dullness and absent air entry were noted at both lung bases. There was no edema. Much protein was found in the urine (7.0 gm. per L.) and 5 to 8 erythrocytes, 5 to 8 leukocytes and many hyaline and granular casts were seen in the urinary sediment. The hematocrit was 35 per cent, the leukocyte count was 13,800/mm.^{3} (78 per cent neutrophils) and the erythrocyte sedimentation rate was raised. The serum albumin was 2.0 gm. per 100 ml.; the serum globulin was 3.3 gm. per 100 ml., the serum cholesterol was 512 mg. per 100 ml., the serum non-protein nitrogen was 41 mg. per cent and the serum creatinine was 2.2 mg. per 100 ml. Tests of liver function, the serum electrolyte levels and numerous serologic examinations were all normal.

Next day the patient complained bitterly of a constant aching pain in the right upper quadrant of the abdomen, the right loin and the right side of the back. Two days later the pain was more severe and radiated down the loin into the right testicle. The pain was constant, without remission and injections of demerol® gave little if any relief. The patient was lying immobile

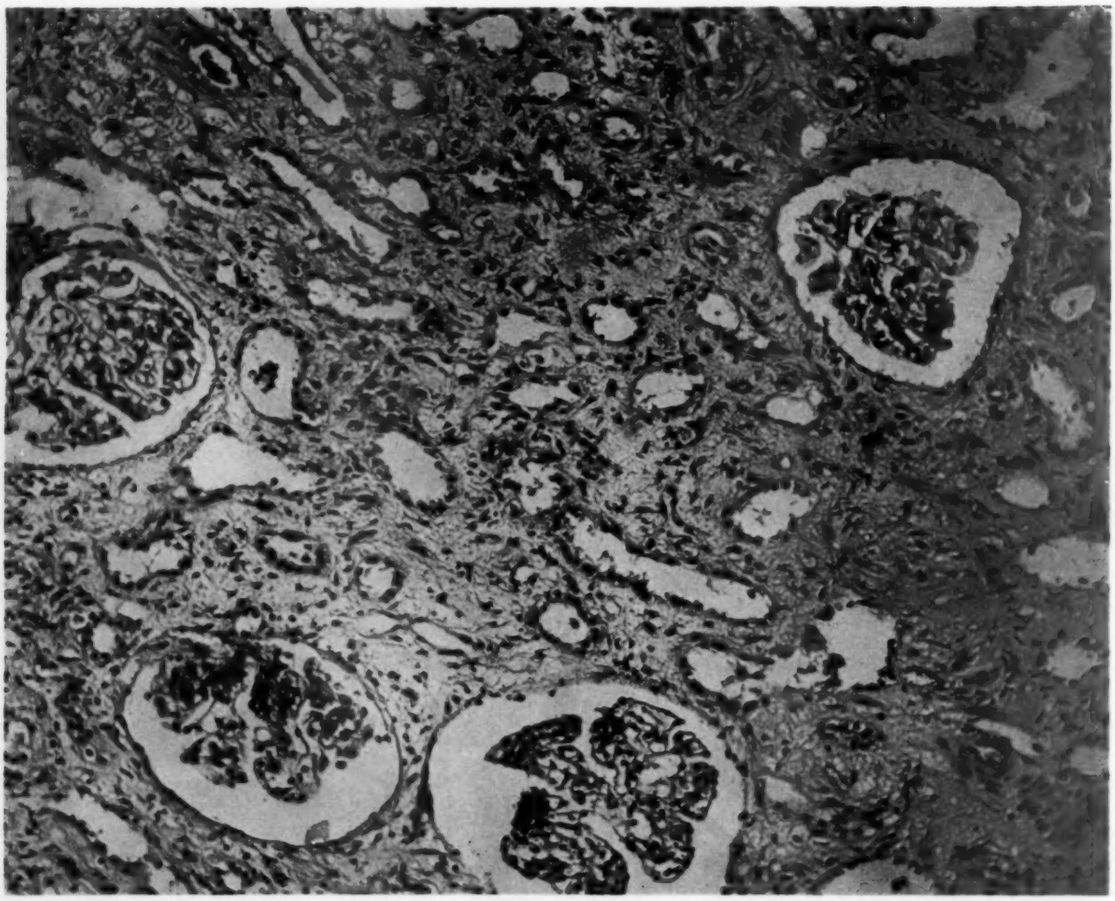


FIG. 4A. First biopsy (November, 1954). There is mild diffuse thickening of the basement membrane of all glomeruli. Note the extremely severe interstitial edema with wide separation and atrophy of the tubules; hematoxylin and eosin, × 160.

in bed, the right flank was bulging, the muscles of the back were in spasm and the whole area was exquisitely tender. The urine contained much protein and on microscopic examination more than 100 red blood cells per high power field and an occasional hyaline cast were seen. The large number of red cells persisted in the urine for forty-eight hours. The leukocyte count was 30,000/mm.^{3} (92 per cent neutrophilis). On October 16 roentgenograms of the abdomen showed that the right kidney, which had previously been normal in size (Fig. 2A), was enlarged (Fig. 2B). Thereafter it increased in size until October 27. (Fig. 2C.)

Because of the fever, sweating, leukocytosis, lumbar pain, tenderness, fullness and muscle spasm, a diagnosis of perinephritic abscess was considered but in view of our experience with a previous case (Pollak et al.[49] Case 1, Table 1), the diagnosis of renal vein thrombosis was also considered. Hemolytic enterococci were grown from the urine. The nonprotein nitrogen was 41 mg./100 ml.; the urea clearance was 31 ml./minute; creatinine clearance 53 ml./minute; and the excretion of phenolsulfonphthalein was 15 per cent in fifteen minutes. The severe pain lasted six days, until October 22. Thereafter it gradually diminished and by October 28 disappeared. On the same day a persistent, mild, aching pain developed in the patient's right groin.

On November 1 a percutaneous biopsy of the right kidney was performed while the patient was in the prone position. (Fig. 4A.)

Eight glomeruli with their surrounding tubules and a small piece of medulla were included in the sections. The glomeruli were large and most of them were ischemic. There was a diffuse but mild regular thickening of the glomerular basement membrane. In periodic acid-Schiff preparations the basement membrane showed increased staining activity; in sections stained by the Mallory technic it appeared red in color. Occasional polymorphonuclear leukocytes were seen in the glomerular capillaries. There were no proliferative changes in the glomeruli. There was very marked edema of the interstitial tissue, and the pale blue staining in hematoxylin-eosin and in Mallory-

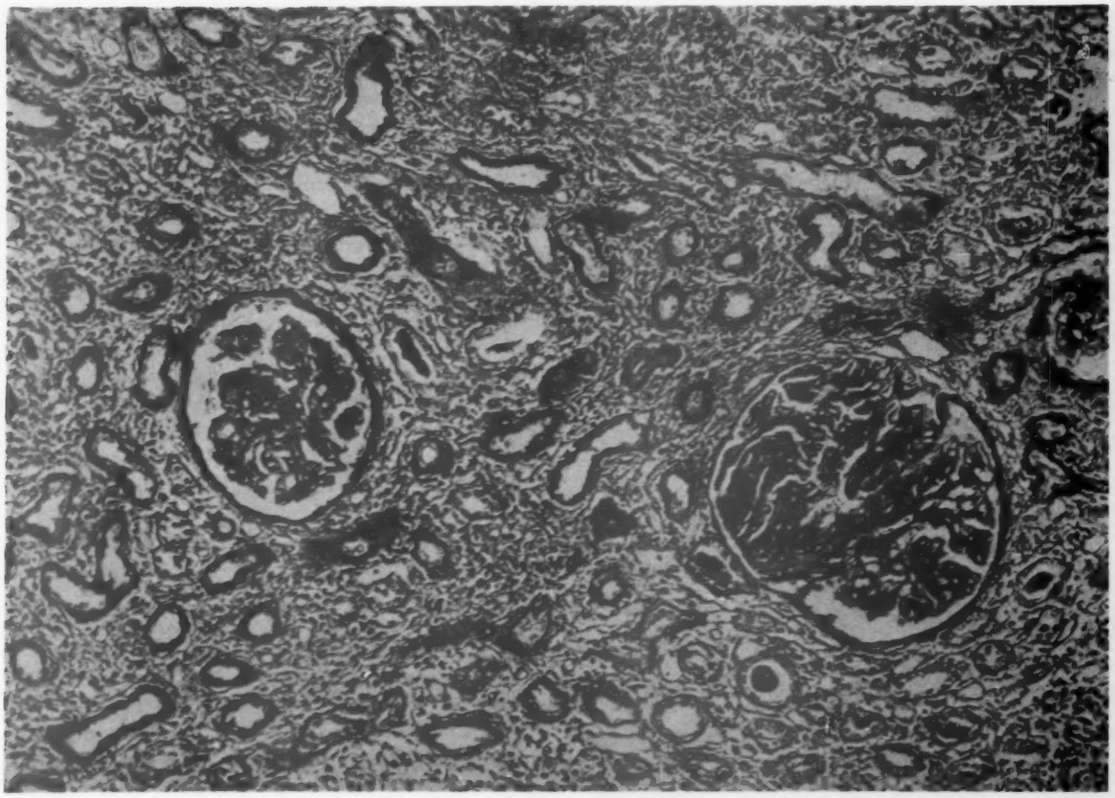


FIG. 4B. Second biopsy (January 10, 1955). There is considerably more thickening of the glomerular basement than in the first biopsy. There is much interstitial fibrosis with moderate infiltration of chronic inflammatory cells. There is a slight degree of edema. The tubules are atrophic and their basement membrane is thickened; periodic acid-Schiff, × 160.

stained sections suggested a pseudomucinous type of degeneration. The fibrillar pattern of the connective tissue was accentuated by this edema. A few acute and chronic inflammatory cells were scattered throughout the interstitial tissue. The convoluted tubules were markedly atrophic. They were lined by flattened epithelium and in oil-red-O stained sections a considerable amount of granular lipid material was noted in the cytoplasm of their lining cells. Proteinaceous material or small hyaline casts were seen in their lumina. The few small arteries in the section did not appear abnormal.

On November 2 gross swelling of the right leg and thigh developed rapidly. This was associated with the pain in the right groin which had become more severe since October 28. The leg swelled to considerable size and edema was very marked. At this time it was believed that thromboembolic phenomena, involving the lungs, renal veins and right common iliac vein, were the most likely cause of his symptoms. Intravenous heparin therapy was therefore started. The next day the patient's temperature fell to just above normal and the urine became almost free of cells and casts. The proteinuria persisted. Two days later the edema extended up the right lateral abdominal wall and the femoral vein was palpated as a cord below the inguinal ligament.

At the time the biopsy was performed, a culture of the kidney tissue was made under sterile conditions and from it hemolytic enterococci—identical with those previously isolated from the urine—were grown. When this information became available a course of penicillin, 10 million units daily, and streptomycin, 1 gm. daily, was started. The patient's temperature promptly fell to normal and the severe sweating attacks ceased.

The swelling of the right leg gradually decreased. Dilated superficial veins were seen on the right leg and on the right side of the abdomen as high as the costal margin. (Fig. 5.) The blood flowed upward in these veins. On November 11 there was pitting edema of the left leg and thigh, which had been increasing gradually in size during the previous week. Two days later they were grossly swollen and evidence of collateral circulation developed on the left side. The swelling thereafter slowly decreased. At this time the urine contained 10.0 gm. protein/24 hours and a moderate number of hyaline and granular casts. Serum non-

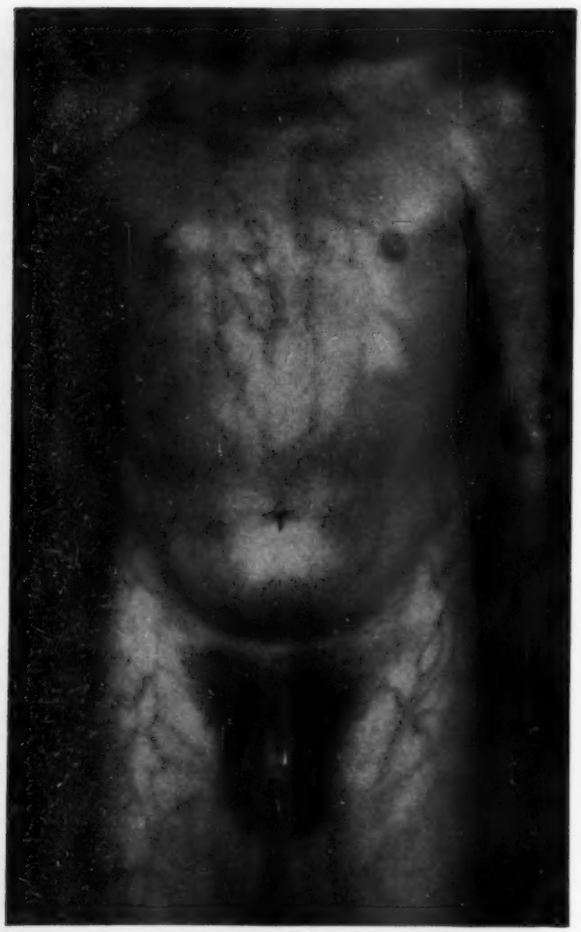


FIG. 5. Infrared photograph of patient B. B. Note dilated superficial venous channels.

protein nitrogen 50 mg. per cent, serum albumin 2.7 gm. per cent.

The patient's clinical condition improved steadily. He continued afebrile, regained his appetite and began to gain weight. By November 29 the urine was sterile and the administration of antibiotics was discontinued. There was persistent gross proteinuria but the urinary sediment was normal and there was no azotemia. Roentgenograms of the chest showed considerable resolution in the areas previously infiltrated (Fig. 3B), and a roentgenogram of the abdomen showed that the previously enlarged right kidney had decreased considerably in size. (Fig. 2D.) The size of the left kidney was unchanged. The edema of the legs had decreased but did not disappear entirely. One week later, however, hemolytic enterococci were again cultured from the urine, and chloramphenicol, 2 gm. daily, with erythromycin, 1.6 gm. daily, was given. Heparin therapy was discontinued on December 22 and the regimen of antibiotics shortly thereafter.

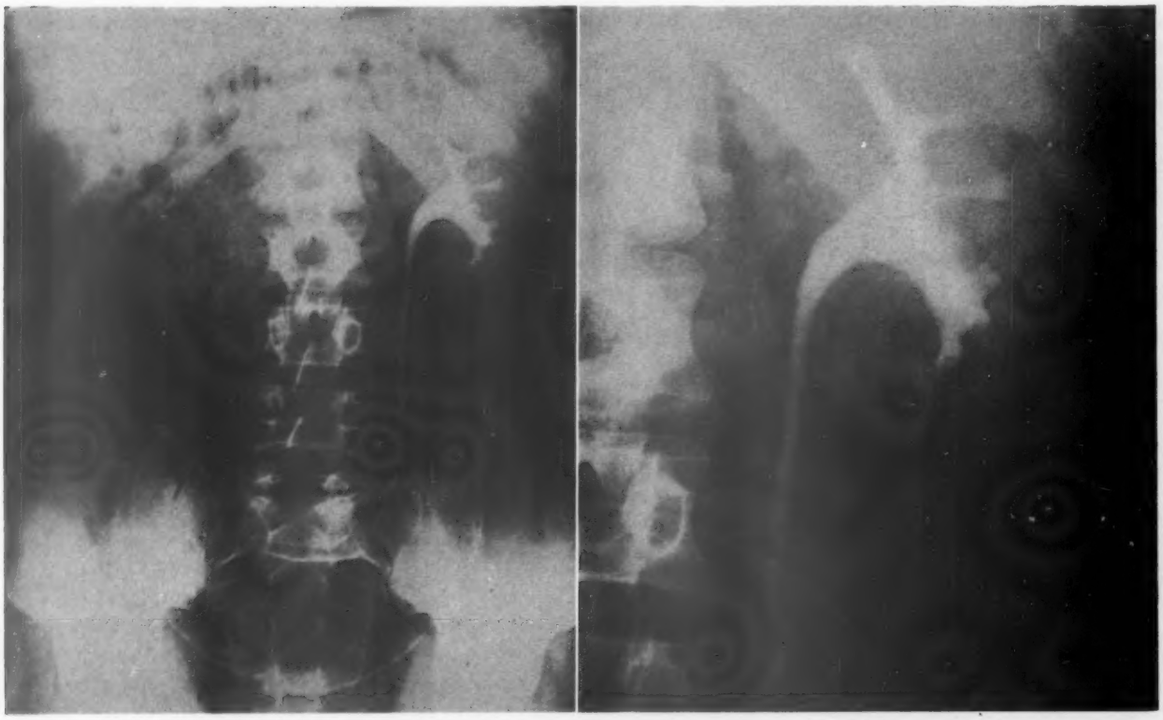
A second renal biopsy was performed on January 10, 1955. (Fig. 4 B.)Thirteen glomeruli with their surrounding tubules and a small piece of medulla were included in the sections. The glomeruli were ischemic. There was considerable diffuse thickening of the glomerular basement membrane, narrowing of the capillary lumina and occasional small areas of fibrosis. The basement membrane was markedly thickened in sections stained with periodic acid-Schiff and was dark blue in Mallory-stained preparations. In some areas features typical of "wire loop lesions"[4] were seen. There was no hypercellularity. Many of the Bowman's capsules were thick and fibrotic and a few Bowman's spaces contained proteinaceous material. There was marked interstitial fibrosis but little edema of the interstitial tissue, which was dark blue in Mallory-stained preparations. There was a marked infiltration of chronic inflammatory cells throughout the interstitial tissue. Tubular atrophy was extreme. The epithelium was flat and the tubular lumina contained proteinaceous material and hyaline casts. The walls of the small arteries were slightly to moderately thickened. Cultures of the renal tissue and of the urine were sterile.

Proteinuria persisted (3 gm. per 24 hours) and the urinary sediment contained a few leukocytes and granular casts. The serum cholesterol was 492 mg. per cent; the serum albumin, 3.1 gm. per cent. Intravenous phlebograms were not obtained because we considered that any trauma to the veins would be sufficient to start the thrombotic process anew. The patient left the hospital on January 12 and was given phenylindandione therapy at home. While at home, edema of the legs and thighs, due to occlusion of both common iliac veins, persisted but was well controlled by elastic stockings and pressure bandages.

In other respects the patient was in good health and his weight gradually increased to 192 pounds. The serum non-protein nitrogen during this period was 51 mg. per cent, the serum albumin, 3.0 gm. per cent, the serum cholesterol, 584 mg. per cent.

On March 14 the patient was readmitted to the hospital for clinical assessment. Except for the persistent edema of the lower limbs the patient was asymptomatic and had had no further thromboembolic episodes. The pulse rate was 84 per minute and the blood pressure was 160/95 mm. Hg. Dilated superficial veins were seen on both legs, on the thighs and on the abdominal wall; there was edema of these regions. The left kidney was easily palpable and appeared to be enlarged. The right kidney was not palpable. Examination of the heart, lungs and central nervous system was within normal limits. Beau's lines were seen on the fingernails.

Analysis of the urine revealed 10.5 gm. protein per 24 hours, a few leukocytes and occasional hyaline and granular casts. Culture of the urine grew hemolytic enterococci. The patient was able to concentrate his urine to a specific gravity of 1.022. The urea clearance was 34 ml. per minute and the creatinine clearance was 95 ml./ml. The excretion of phenol-



6A 6B

FIG. 6A. Intravenous pyelogram in patient, five months after sudden thrombosis of the right renal vein, and eight months after partial and gradual thrombosis of the left renal vein. Note excellent function of slightly enlarged left kidney. The small right kidney is not functioning.

FIG. 6B. Detail of (A). Note serrated, scalloped or varicose appearance of pelvis and ureter (left) due to dilated collateral venous drainage from the kidney.

sulfonphthalein was 22 per cent in fifteen minutes. The hematocrit was 46 per cent; the leukocyte count was 10,800/mm.^{3} The blood creatinine was 1.6 mg./100 ml., the blood urea nitrogen was 14 mg./100 ml. and the non-protein nitrogen was 30 mg./100 ml. The serum albumin was 2.4 gm./100 ml. and the serum globulin was 1.9 mg./100 ml.

On March 19 an intravenous pyelogram was obtained. (Fig. 6.) The right kidney was small and failed to excrete any dye. The left kidney was enlarged and the excretion of dye was prompt and excellent. The left ureter appeared roughened; this appearance extended to the pelvis. It was thought to be due to dilated ureteric veins. Roentgenograms of the chest showed residual fibrotic changes. The patient was seen in consultation. Cystoscopy was performed on March 31. Only the right ureter was catheterized but no urine was obtained from it in a four-hour period. The pelvis of the right kidney appeared normal when outlined with dye through the ureteric catheter.

The patient was discharged from the hospital on April 1 and was treated with the anticoagulant drug dipaxin® (2-diphenylacetyl-1, 3-indandione). He remained in excellent health but was readmitted on May 19.

On the third hospital admission physical examination was unchanged. The blood pressure was 160/98 mm. Hg and the enlarged left kidney was easily palpated. Cystoscopy was repeated. No urine came from the right ureter. Five minutes after intravenous injection, indigo carmine appeared in good concentration but only from the left ureter. The urine contained 7.9 gm. protein per twenty-four hours. Eight to ten red blood cells, five to six white blood cells and a few fatty casts and doubly refractile bodies were seen in each high power field. The serum non-protein nitrogen was 43 mg. per cent, serum cholesterol 630 mg. per cent, serum albumin 2.7 gm. per cent.

The administration of dipaxin was discontinued and heparin was substituted. On May 31 a right nephrectomy was performed. A single large venous collateral channel with its tributaries was seen in the perinephric fat. (Fig. 7.) Many fibrous adhesions were found in the perinephric fat. These were attached to the renal capsule and were so numerous and dense that removal of the kidney with its capsule intact was impossible. The capsule was incised and stripped from the kidney. The renal pedicle was very firm, short, solid and cord-like and could not be dissected out. It was cut across and left *in situ* when the kidney was removed.

The kidney weighed 97 gm. and measured 9.5 cm.

in length, 4 cm. in thickness and 5 cm. in width. The capsule and pelvis had been removed at the operation. The external surface was slightly nodular. It was hard and cut like solid gutta-percha. The cut surfaces were very firm and greyish pink in color. The corticomedullar margins were fairly distinct. The tips of

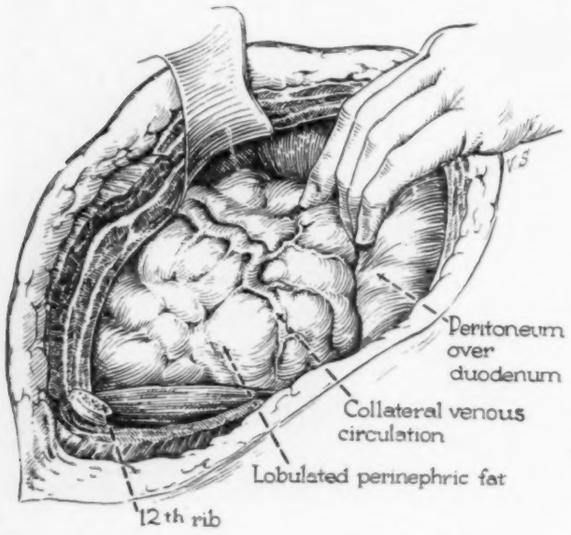


FIG. 7. Drawing of operative exposure of right renal area. Note lobulated perinephric fat and single large collateral venous channel.

the pyramids were firm and greyish white in color. Abundant yellow-grey fat was seen around the renal pelvis. The perirenal fat was firm and appeared to be infiltrated by fibrous tissue. There was no evidence of renal or retroperitoneal hematomas.

A histologic examination revealed most of the glomeruli were congested. (Fig. 8.) There was considerable diffuse thickening of the glomerular basement membrane. An occasional glomerulus was partially hyalinized. Some of Bowman's capsules were distinctly sclerosed and thickened and Bowman's spaces contained proteinaceous material. Dense interstitial fibrosis and extreme tubular atrophy was seen. In both the cortex and medulla the interstitial tissue was infiltrated by large numbers of chronic inflammatory cells. The atrophic tubules contained proteinaceous material and hyaline casts. Widely scattered throughout the section were a few tubules containing a considerable amount of fine granular lipid in their cytoplasm. These were the tubules in which the cells were the least atrophic. There was mild thickening and fibrosis of the walls of several small arteries. Several veins were occluded by organizing thrombi.

The operation was well tolerated. Therapy with intravenous heparin had been discontinued four hours preoperatively and was reinstituted two hours after the operation. The postoperative course was uneventful. On the seventh postoperative day heparin therapy was terminated and oral dipaxin was substituted.

When discharged from the hospital two weeks later, the patient had recovered from the operation and the only residual disability was persistent edema of the legs. This was well controlled by elastic stockings. The patient was able to concentrate his urine to a specific gravity of 1.025; 17.3 gm. and 13.7 gm. of protein were excreted in two twenty-four-hour specimens. The urinary sediment contained 1 to 2 leukocytes and a few granular and fatty casts. Only a few micrococci were cultured from the urine. The excretion of phenolsulfonphthalein was 19 per cent in 15 minutes; the urea clearance was 34 ml./min. and the creatinine clearance was 65 ml./min. The total serum protein was 5.2 gm./100 ml. (albumin 2.7 gm., globulin 2.5 gm.); the blood creatinine was 2.0 mg./100 ml.; the blood urea nitrogen 20 mg./100 ml., the nonprotein nitrogen 43 mg./100 ml. and the blood cholesterol was 400 mg./100 ml. The chloride was 103 mEq./L. and CO_2 was 28 mM./L.

When last seen in September, 1955 the patient was in excellent health and was working full time as a clerk and salesman. The residual edema of his legs was well controlled by elastic stockings. The blood pressure was 140/95 mm. Hg. The blood creatinine was 1.4 mg./100 ml., and the non-protein nitrogen was 30 mg./100 ml.; the serum albumin was 2.7 gm./100 ml.; the serum globulin was 2.2 gm./100 ml. and the serum cholesterol was 640 mg./100 ml. The urine from the left kidney contained leukocytes and hyaline and granular casts and 12 to 18 gm. protein per twenty-four hours. The prothrombin level was easily maintained in the therapeutic range by dipaxin.

Diagnosis. From the beginning the nature of this patient's illness was difficult to determine. Numerous diagnoses had been considered and were found wanting. The association of the nephrotic syndrome with recurrent pleuritic pain, increasing pulmonary infiltration and dyspnea with fever and loss of weight, was distinctly unusual. Glomerulonephritis, amyloidosis and systemic lupus erythematosus had been considered as possible causes of the nephrotic syndrome. At the time of admission to the University of Illinois Hospitals the patient began to cough up blood. This suggested that the infiltrations in the lungs, previously thought to be pneumonic in nature, were due to recurrent pulmonary infarctions.

When severe pain suddenly developed in the patient's right loin and was associated with tenderness, fullness, muscle spasm and the appearance of a mass, a mechanical disturbance of the renal circulation seemed possible. Because of fever, sweating, loss of weight, high leukocytosis and the presence of bacteria in the urine, a diagnosis of staphylococcal fever of Ryle[55] and perinephric abscess was seriously considered. It will be recalled that Vallery-Radot[64] made a diagnosis of perinephric abscess in his patient with

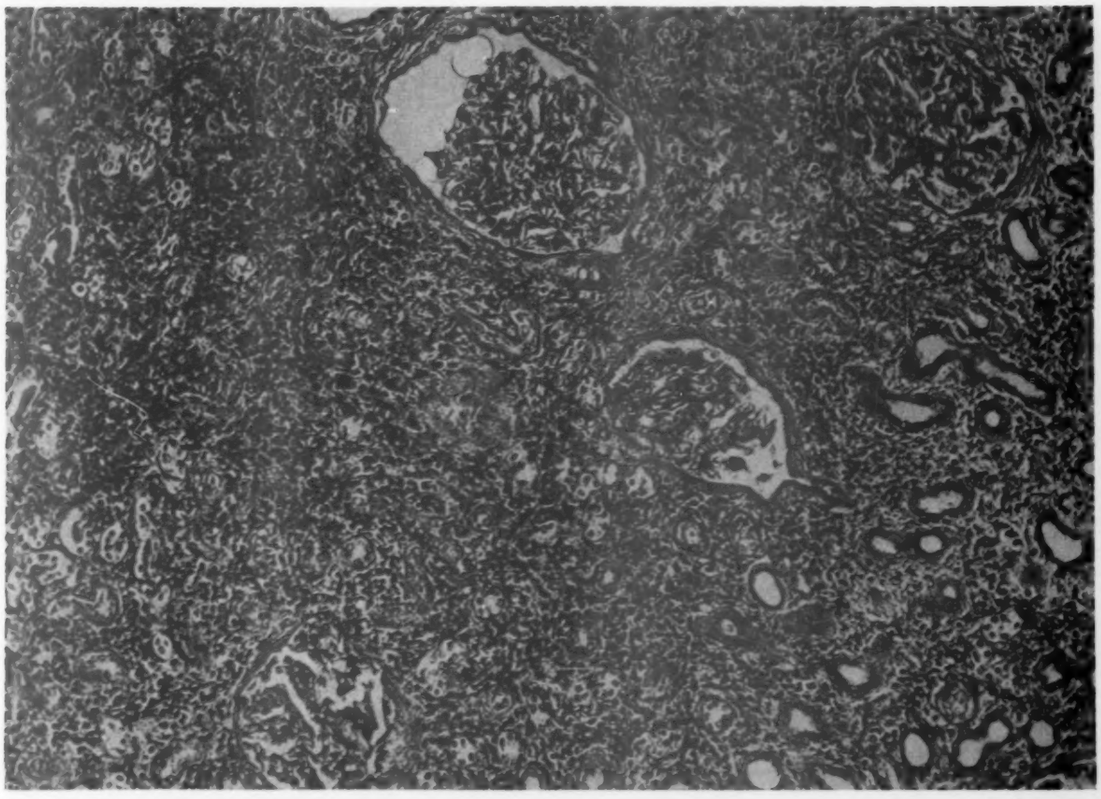


FIG. 8A. Surgical specimen (May 31, 1955). The glomeruli are congested and their basement membrane is thickened. There is proteinaceous material in some Bowman's spaces. Note the severe interstitial fibrosis and infiltration with chronic inflammatory cells. Tubular atrophy is striking; hematoxylin and eosin, × 160.

renal vein thrombosis and an exploratory operation was performed. However, in our patient the diagnosis of thrombosis of the right renal vein was considered to be more likely because of the pain, swelling and tenderness in the right loin, and the strikingly rapid and extraordinary enlargement of the right kidney which was evident on the roentgenogram. The previous history of prolonged left flank pain and tenderness followed by enlargement of the left kidney as revealed by roentgenograms, the nephrotic syndrome and the history of recurrent pulmonary infarctions, made a diagnosis of widespread thromboembolic disease certain and a diagnosis of bilateral renal vein thrombosis probable. Two further events confirmed this diagnosis. The renal biopsy specimen was similar to that seen in our first case[49] and manifest thromboses developed one after the other in the right common iliac, external iliac and femoral veins.

Effects of the Renal Vein Thromboses. The symptoms relating to the two episodes of thrombosis of the renal veins were similar in nature. However, they were far more acute and insistent when the right kidney was involved in October 1954. The severity of these symptoms was due to the very rapid enlargement of the kidney to approximately four times its normal size. We believed that this was the result of a sudden and complete occlusion of the right renal vein. By contrast, it seemed that the earlier occlusion of the left renal vein in August 1954 was a gradual and incomplete process. These conclusions are consistent with the results of experiments on the ligation of renal veins. When the vein is ligated completely in animals the kidney becomes engorged and greatly swollen, reaching its maximum size in about five days.[2,11,12,25,45,48,53] Thereafter, atrophy of the kidney gradually takes place and is complete in 100 to 130 days. In our patient the changes observed in the right kidney (Fig. 2) followed a course similar to that observed in animals. Radiologically the kidney increased rapidly in size; after about ten days it began to decrease in size. Five months after the occlusion it was atrophic and completely functionless. At operation only a single large collateral venous channel was found on this side.

When the occlusion of the renal vein is incomplete and develops gradually, there is time for an extensive collateral circulation to develop through the capsular, ovarian or spermatic, lumbar, suprarenal and ureteral veins.[11,54] The presence of dilated pelvic and ureteral veins on the intravenous pyelogram (Fig. 6) indicates that such a collateral circulation did develop from the left kidney of our patient. The collateral circulation

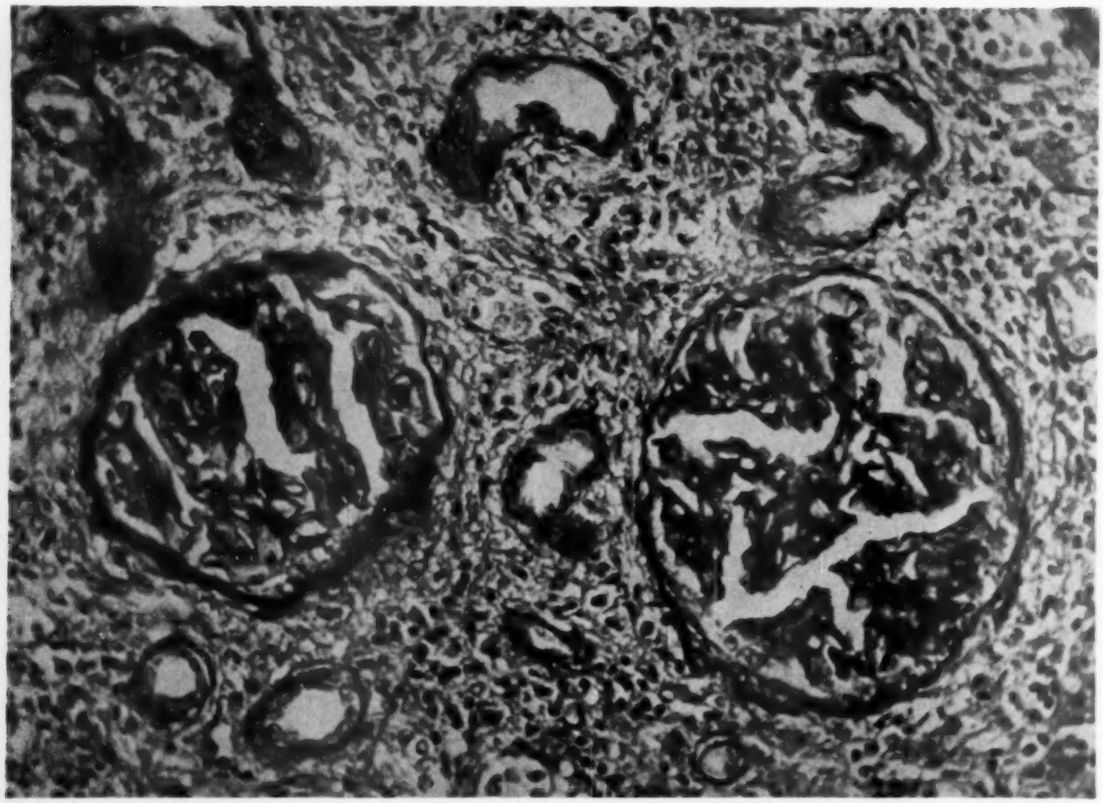


FIG. 8B. Higher magnification showing glomerular basement membrane thickening; periodic acid-Schiff, × 320.

which developed as a result of slow or incomplete occlusion of the left renal vein allowed for the maintenance of excellent renal function, even after the function of the right kidney was totally lost.

The nephrotic syndrome supervened, indicating that this can occur as a result of damage to only one kidney in the presence of a normally functioning second kidney. In this regard Dr. Blainey[7] informed us of another case in which the nephrotic syndrome supervened after thrombosis of the left renal vein.

Treatment. As soon as the diagnosis of thromboembolic disease was firmly established, treatment with intravenous heparin was initiated. As a result the temperature decreased and there was a partial clearing of the urinary abnormalities. Hemolytic enterococci had been cultured from the urine and the same organism grew in the culture of the renal tissue which was obtained by biopsy. The idea that the renal infection was superimposed on the congested edematous kidney was consistent with the work of Nisio.[44] He injected Escherichia coli intravenously into dogs in which the renal veins were partially occluded. He observed that if the injection was made before tying the vein, bacilli were found in the urine from the affected kidney for a period of seven days. If the injection was made after the renal vein was tied, the organism became implanted in the kidney in all cases and pyelonephritis or abscess formation followed.

Soon after the administration of penicillin and streptomycin the patient became afebrile and the urinary sediment cleared. From this point onward he made an uninterrupted clinical improvement, the blood creatinine and nonprotein levels gradually fell to normal and the pulmonary infiltrations cleared.

Reasons for Nephrectomy. The non-functioning atrophic right kidney was removed for the following reasons: it was the site of infection with hemolytic enterococci, which two extensive courses of antibiotics had failed to eradicate. It was a possible source for the spread of infection or for the commencement of new thromboses. There was a possibility that hypertension might persist as a result of the chronic infection and circulatory changes in the kidney. The blood pressure had varied from 140/90 to 170/100 mm. Hg, and any further elevation might compromise the function of the left kidney. Braun-Menendez[9,10] and Friedberg[22] noted the development of hypertension in a proportion of dogs in which the renal veins had been ligated, and Perry and Taylor[47] reported a case of fatal hypertension following thrombosis of the inferior vena cava and both renal veins. In our patient the function of the left kidney was good and has remained so since the operation.

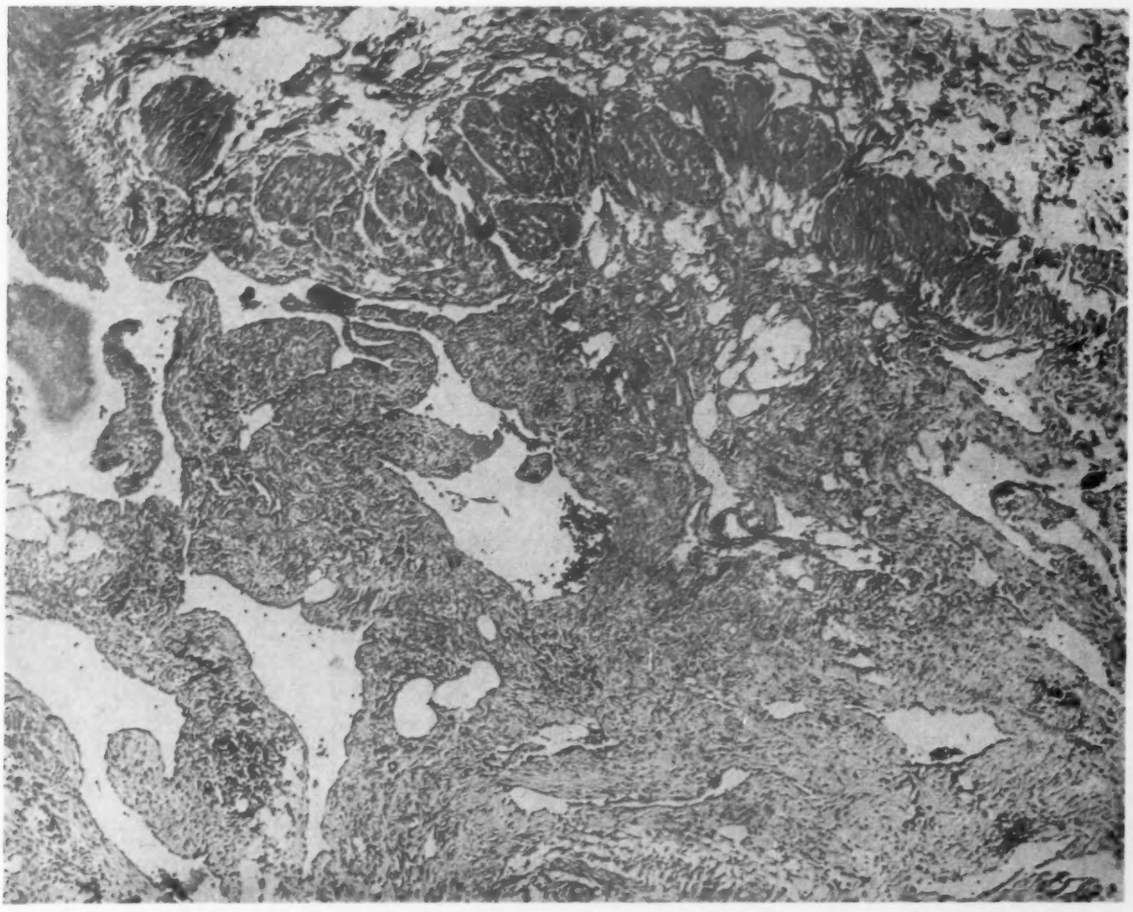


FIG. 8C. Cross section through a large renal vein near the hilus of the kidney. Note the smooth muscle of the media in the upper portion of the picture. The lumen of the vein is obliterated by a well organized and recanalized thrombus; hematoxylin and eosin, × 80.

Prognosis. As the patients in all the previously reported cases of renal vein thrombosis with the nephrotic syndrome have died, we have little basis on which to make a prognosis. Shattock's patient,[87] despite persistent edema and proteinuria, lived an active life for twenty-five years following sudden occlusion of the inferior vena cava and renal veins. At present our patient, despite persistence of proteinuria and edema of the legs, has returned to work. His prognosis depends on the functional capacity of the left kidney, the possibility of further damage to the left kidney by infection or hypertension and the chances of recurrence of thromboembolism.

COMMENTS

Clinical Features of Renal Vein Thrombosis with the Nephrotic Syndrome. In any condition in which signs and symptoms are due to mechanical obstruction of blood vessels, it is likely that their nature and severity will vary with the rapidity of onset and the degree of obstruction. Thus we cannot expect to find a uniform clinical picture. In 1934 Hepler[27] reviewed forty cases of renal vein thrombosis without the nephrotic syndrome. In twenty-two cases there were definite symptoms referable to the kidney—sudden onset of hematuria, lumbar pain and tenderness and enlargement of the kidney. Despite this Hepler was forced to conclude that "in no instance has a diagnosis (of renal vein thrombosis) ever been made with pathologic confirmation." Renal vein thrombosis may or may not be associated with the nephrotic syndrome. Analysis of our own cases, together with those reported in the literature, leads us to believe that, in a significant proportion at least, the syndrome is sufficiently characteristic to permit clinical diagnosis.

The clinical features of the reported cases of renal vein thrombosis with the nephrotic syndrome appear in Table 1, together with those in

TABLE 1

CLINICAL FEATURES OBSERVED IN CASES OF RENAL VEIN THROMBOSIS WITH THE NEPHROTIC SYNDROME

Source	Age and Sex	Preceding Symptoms	History of Occlusion of Renal Veins	Duration of Symptoms of Renal Vein Thrombosis	Other Areas of Thrombosis	Serum		Urine		Remarks
						Protein (gm./100 ml.)	Cholesterol (mg./100 ml.)	Protein	Red Blood Cell Count (per high power field)	
1. Rayer (1840)	57 M	.....	Lumbar pain; edema disappeared and recurred; recurrence of pain; edema became generalized	1 year	.....	.....	.....	Abundant precipitate	.....	Phthisis which led to death
2. Delaruelle (1846)	26 F	Pleurisy	Persistent abdominal pain followed immediately by generalized edema; no pain in lumbar region	21 days	Right and left lungs	.....	.....	Persistent large amount	.....	Death due to uremia
3. Vidal (1854)	12 M	Weakness, abdominal pain and colic; anorexia, diarrhea, wasting	Generalized edema; pain in the region of the kidneys; abdomen tender	17 days	Crural and internal saphenous	.....	.....	Heavy proteinuria	.....	.....
4. Neu (1922)	12 F	Fatigue, malaise, nausea	Nausea, thirst; edema of legs; oliguria; generalized edema	40 days	.....	.....	.....	8.5 gm./L.	.....	Death due to uremia
5. Heilmeyer and Lippross (1937)	52 M	Anorexia, nausea	Pressure under left costal margin; 2 days later generalized edema; tenderness over both kidneys. I.V.P.: large kidney with poor visualization on right; no visualization on left	40 days	.....	6.9	.....	15 gm./L.	Fluctuating number	Death with oliguria and uremia
6. Derow et al. (1939)	15 M	.....	May, 1935: costovertebral pain and tenderness on left. Aug., 1935: costovertebral pain, tenderness, muscle spasm on right: pain radiated to groin. March, 1936: generalized edema; I.V.P.: large kidneys; moderate excretion of dye	16 mos.	Right thigh; right external jugular; ascites and collateral circulation on abdomen	A 1.5 G 2.0	926	+++	20 to 30 when he had pain	Died of acute gastrointestinal infection
7. Moschcowitz (1948), Gerber and Mendlowitz, (1949)	43 M	Right and left pleurisy; swelling and induration of right leg, flank and buttock, followed by similar affection on left. Right external jugular thrombosis	18 mos. after edema of legs appeared, it increased and became generalized	8 mos.	Right and left lungs; veins from legs; external jugular; axillary	A 1.6 G 2.1	735	+++	.....	Died of erysipelas
8. Vallery-Radot et al. (1949)	47 F	Fall from bicycle led to lumbar pain. One month later edema and proteinuria	Lumbar pain; generalized edema; later recurrence of very severe pain followed by oliguria, anuria; tenderness, resistance; thought to be a perinephic abscess and operated on	3 mos.	.....	4.8	600	10 gm./L.	+	Recurrence of pain led to sudden deterioration and death with anuria and uremia
9. Shulman et al. (1950)	67 M	Two myocardial infarcts; severe congestive cardiac failure	Generalized edema; I.V.P.: good excretion	2 mos.	.....	A 0.5	1200	7 gm./L.	.....	Died with uremia

TABLE 1 (*Continued*)

Source	Age and Sex	Preceding Symptoms	History of Occlusion of Renal Veins	Duration of Symptoms of Renal Vein Thrombosis	Other Areas of Thrombosis	Serum		Urine		Remarks
						Protein (gm./100 ml.)	Cholesterol (mg./100 ml.)	Protein	Red Blood Cell Count (per high power field)	
10. Miller et al. (1950)	18 M	.....	Pain in right lower quadrant and nausea; normal appendix removed; 7 days later massive anasarca appeared	2 mos.	Left leg and pelvis	A 1.2 G 2.1	860	26 gm./24 hrs.	5 to 10	.....
11. Blainey et al. (1954) Case 1	72 M	Edema of legs	Edema of legs later became generalized; no abdominal pain	3 mos.	Lung	A 1.6 G 2.6	340	14 gm./24 hrs.	.....	Died of pulmonary infarction
12. Blainey et al. (1954) Case 2	55 F	Femoral vein thrombosis	Generalized edema	8 mos.	Anastamotic channels over abdominal wall	A 1.5 G 3.8	390	15 gm./24 hrs.	.....	Died with uremia
13. Dean (1955)	54 F	Pain and swelling in thighs; mitral stenosis auricular fibrillation	Increasing edema	3 mos.	Axillary artery embolus	A 0.8 G 2.7	400	12 gm./L.	0	.....
14. Blainey (1955)	34 M	.....	Severe pain in left side and loin; generalized edema one week later	.....	.....	A 1.1 G 3.1	.....	.....	.....	Enlarged non-functioning left kidney removed as it was thought to be hypernephoma; extensive thrombus found in renal vein
15. Pollak et al. Case 1*	29 M	Congestive cardiac failure; cerebral embolus	Severe constant epigastric pain; later severe pain in the right side of the abdomen; gradual onset of generalized edema; later fullness, tenderness and a mass in right upper quadrant	6 mos.	.....	A 1.4 G 4.8	1200	.....	120	Died from massive gastrointestinal tract hemorrhage
16. Pollak et al. Case 2	35 M	Multiple pulmonary emboli	Severe pain in left loin radiating to the testicle; followed by generalized edema; later severe pain, fullness, tenderness and mass in right loins; right kidney enlarged greatly on x-ray and later became very small	Still alive	Both lungs; both common iliac veins	A 2.0 G 3.3	512	16 gm./24 hrs.	100	Right kidney became atrophic and was removed; large well functioning left kidney

* This case will be reported in full by Dr. Benjamin M. Kaplan et al.

the two patients we have studied and in two other unreported cases.[7,13]

Pain. Of the sixteen cases, seven patients had pain in the loin, one had persistent generalized abdominal pain and one had persistent pain in the abdomen and loin. In the two patients who suffered from abdominal pain thromboses of the inferior vena cava as well as the renal vein were evident. In most patients the pain was very severe, resembling renal colic in its intensity and radiation to the groin or testicles. Unlike renal colic, however, it was not paroxysmal but continuous. The pain frequently interfered with sleep and narcotic agents failed to relieve it.[1,34,52] In seven of the nine patients the onset of pain was followed very shortly by the appearance of generalized edema.

Swelling. The kidney itself is insensitive to painful stimuli but distention of its capsule is painful. The increase in the size of the kidney and the distention of its capsule, consequent upon sudden occlusion of the renal vein, accounts for the pain and the tenderness, the fullness and the appearance of a mass in the loin, as well as for the gross enlargement of the kidney seen on examination of the roentgenograms. This gross enlargement was graphically described by Vallery-Radot,[64] who stated that at operation his patient's kidney looked like an eggplant. When the patient died a few days later, the kidneys weighed 880 and 850 gm. (normal 150 to 200 gm.). If occlusion of the renal vein is gradual or partial, all the symptoms described above may be mild or absent. Pain in the flank, however, should draw attention to the kidney.[34]

Urinary Findings. Hematuria has been reported inconstantly. It may be gross or microscopic. In animals, however, it is apparent in almost all instances after the renal vein has been ligated.[12,17,54] In both of our patients hematuria occurred for a few days at the time of occlusion of the renal veins; and in B. B. more than one hundred erythrocytes were found in the centrifuged urine specimen for a brief period of forty-eight hours only. Thus it may appear transiently in the urine and may not be recognized.

In all sixteen cases protein was found in large amounts in the urine and persisted until death. This proteinuria and the tubular atrophy and degeneration are the cause of the casts in the urine.

Thromboembolic Phenomena. In twelve of the sixteen cases (Tables I and II) there was clinical or pathologic evidence of thromboembolic phenomena, most commonly in the pulmonary vessels, the inferior vena cava or the veins of the legs. Three of the six cases of "visceral thrombophlebitis migrans" reported by Gerber and Mendlowitz[23] had thrombosis in the renal veins. Fever, sweating and leukocytosis, so common in infectious diseases, are likewise common manifestations of thromboembolism.

Diagnosis. From the data presented a characteristic syndrome may be delineated: the patient is suddenly seized with pain in the loin; this pain is constant and persistent. It is moderately severe at first but within a few days becomes exquisitely painful. This pain interferes with sleep and little relief is afforded by narcotics. It often radiates to the groin or testicle and may persist for a week or longer. The patient looks and feels acutely ill, is feverish and has a leukocytosis. On examination there is fullness, tenderness and muscle spasm in the loin. When this is overcome, a mass is felt and on x-ray of the abdomen the affected kidney is seen to be enlarged. Much protein is found constantly in the urine. Hematuria is often transient and should be sought for diligently. Often there is evidence of thromboembolism in the lungs, pelvis, limbs and elsewhere. The nephrotic syndrome develops in adults and appears soon after the onset of symptoms.

At the other end of the clinical spectrum are those patients in whom the veins are occluded so gradually that many or all of the described symptoms may be of a milder degree or absent, and the nephrotic syndrome may be the only clinical manifestation of the renal vein thrombosis. In between are those cases who present with the nephrotic syndrome and evidence of thromboembolism.

Differential Diagnosis. Renal vein thrombosis should be distinguished from renal arterial occlusion, perirenal hematoma, perinephric abscess, involvement of the inferior vena cava by direct spread of a carcinoma of the kidney and any disease process which causes a considerable increase in pressure within the inferior vena cava. In cases presenting with the nephrotic syndrome of uncertain etiology the diagnosis of renal vein thrombosis must be considered, and inquiry should be made for symptoms of renal vein occlusion or of thromboembolism elsewhere. In these patients renal biopsy is of material help in making the diagnosis, as are serial x-ray studies of the kidney (Fig. 2) and infra-red photographs, which bring out the venous dis-

TABLE II

SOME PATHOLOGIC FEATURES OBSERVED IN CASES OF RENAL VEIN THROMBOSIS WITH THE NEPHROTIC SYNDROME

Source	Age and Sex	Vascular Thromboses						Kidneys	Lungs	Other Features
		Inferior Vena Cava	Portal System	Veins of Legs	Renal Veins	Pulmonary Veins and Arteries	Veins Elsewhere			
1. Rayer (1840)	57 M	.....	.....	.....	Recanalized clot of long standing in both veins	.....	.....	Weight 180 and 240 gm.; kidneys large and soft; cortex and medulla, easily separated	Tuberculosis with cavitation	.....
2. Delaruelle (1846)	26 F	Clot from common iliacs to above renal veins	.....	.....	Clot in right, adherent to inferior vena cava—occlusion incomplete; complete occlusion on left	.....	.....	Smooth yellow, fatlike; twice normal size	Small infarctions	.....
3. Vidal (1854)	12 M	.....	.....	Right and left crural, left external iliac and internal saphenous	Inflamed walls; purulent adherent clot in branches; left completely blocked; right extends to primary divisions of veins	.....	.....	Enlarged yellow, with pale cortex	Engorged and indurated	Large purulent mass extending over first seven dorsal vertebrae which are partially destroyed
4. Neu (1922)	22 F	.....	.....	.....	Thickened wall; firm adherent clot extending into inferior vena cava on left	.....	.....	Weight 200 and 250 mg.; surface reddish yellow; congested veins; amyloid deposits	.....	Terminal pericarditis; amyloid in spleen
5. Heilmeyer and Lippross (1937)	52 M	.....	.....	.....	On right thrombi in main vein and branches; the left is a whole cast of thrombus, extending into interlobular veins	Right pulmonary artery	.....	Large, smooth, yellow; possible underlying glomerulonephritis	.....	.....
6. Derow et al. (1939)	15 M	Occluded from junction of common iliacs to just distal to hepatic veins	Portal, splenic, and superior and inferior mesenteric	.....	Occluded from inferior vena cava to hilus of the kidney; branches patent; thrombi of varying age	.....	.....	Weight 360 and 360 gm.; large and smooth with congested surfaces	Normal	Died of pneumococcal peritonitis
7. Moschcowitz (1948); Gerber and Mendlowitz (1949)	43 M	Cavernomatous from hepatic to femoral veins	Superior mesenteric, splenic	Common iliacs and femorals	Both firmly recanalized; recent clot in the left	Artery to right upper lobe	Left adrenal and spermatic	Large pale yellow gray with medullary congestion	Old infarcts	.....
8. Vallery-Radot et al. (1949)	47 F	.....	.....	.....	Bilateral thrombosis to the level of the hilus	.....	.....	Kidneys of enormous size 850 and 880 gm.; the renal capsule was thick and infiltrated with blood; massive infiltration with blood had destroyed normal architecture	.....	.....
9. Shulman et al. (1950)	67 M	Thick, opaque intima	.....	.....	Organizing adherent thrombus in hilus; thrombi old in radicles; recent in main veins	.....	.....	Weight 325 and 360 gm.	Normal	Old myocardial infarcts and infarcts of the spleen
10. Miller et al. (1954)	18 M	.....	.....	.....	Thrombi from mouth of renal veins to small radicle	Pulmonary arteries	.....	Weight 295 and 390 gm.; smooth white surface; few areas if mottling	Thrombi in vessels	Periarteritis nodosa in testes, liver, pancreas, but not in kidney
11. Blainey et al. (1954) Case 1	72 M	Organized thrombus	.....	Femorals and iliacs	Both completely obstructed; clot contiguous with that in inferior vena cava	Multiple arterial occlusions	Ureterics	Thrombi in many arcuate and interlobular veins; many recanalized	Several old and one recent infarct	.....
12. Dean (1955)	54 F	Renal to common iliac veins	.....	Femorals	Both renal veins	In many arteries	Ovarians; axillary artery	Normal size and slightly congested	.....	Several arterial thrombi
13. Pollak et al. (1955) Case 1	29 M	Below hepatic veins to above junction of common iliacs	.....	.....	Both renal veins extending to inferior vena cava	Multiple arterial occlusions	.....	Weight 220 and 220 gm.; pale yellow surface with irregular cortex	Multiple pulmonary infarcts; small abscesses in right lower lobe	.....

TABLE III

ANALYSIS OF HISTOLOGY OF THE KIDNEY IN RENAL VEIN THROMBOSIS WITH THE NEPHROTIC SYNDROME*

Source	Autopsy or Biopsy or Surgical	Duration Prior to Histological Study of Kidney (mos.)	Glomeruli				Bowman's Capsule	Protein in Bowman's Space	Tubules			Tubular Lumina			Interstitial Tissue				Vessels
			Basement Membrane	Cellularity	Polymorphonuclear Leukocytes in Lumen of Capillaries	Blood in Capillaries			Atrophy	Dilation	Epithelium	Protein	Cells	Casts	Edema	Fibrosis	Congestion	Cellular Infiltration	
Derow (1939)	A	16	Diffuse thickening	Normal	Nil	Slight ischemia	Slight thickening	0	Patchy	Patchy	Flat	+	0	+	Moderate diffuse	Patchy	0	Patchy	Marked congestion; small hemorrhages
Moschcowitz (1948); Gerber and Mendlowitz (1949)	A	3	Normal	Slight increase	Nil	Varies from increase to ischemia	Normal (and arteriosclerotic scars)	0	Patchy	Marked	Flat; contains lipid	+	0	+	Slight	Patchy	0	Foci	Congestion of capillaries; thickening, edema and sclerosis of veins with intimal proliferation
Vallery-Radot et al. (1949)	A	⅓	Moderate, diffuse thickening	Normal	Nil	Slightly congested	Normal	0	Marked	Slight	Mild degeneration	+	0	+	Much	Slight	Much	Nil	Arteriosclerosis; recently thrombosed vein undergoing organization
Blainey et al. (1954)	A	3	Diffuse severe thickening; "wire loops"; narrowing of capillary lumens	Normal	+	Congested	Slight thickening (and arteriosclerotic scars)	0	Slight	.....	Degeneration	+	0	+	Moderate, diffuse	Slight	0	Foci	Arteries thickened, walls hyalinized; thickening fibrosis and edema of wall of veins and intimal proliferation; antemortem thrombus in main renal veins
Dean (1955)	A	3	Diffuse marked thickening; "wire loops"; narrowing of capillary lumens	Normal	Nil	Ischemic	Slight thickening (and arteriosclerotic scars)	0	Moderate to severe	Focal	Flat	+	0	+	Moderate, diffuse	Moderate, focal	0	Small foci	Mild arteriosclerosis; few veins occluded by organized or recanalized thrombus

TABLE III (*Continued*)

Source	Autopsy or Biopsy or Surgical	Duration Prior to Histological Study of Kidney (mos.)	Glomeruli				Bowman's Capsule	Protein in Bowman's Space	Tubules			Tubular Lumina			Interstitial Tissue				Vessels
			Basement Membrane	Cellularity	Polymorphonuclear Leukocytes in Lumen of Capillaries	Blood in Capillaries			Atrophy	Dilation	Epithelium	Protein	Cells	Casts	Edema	Fibrosis	Congestion	Cellular Infiltration	
Pollak et al. (Case 1)	B	5	Mild, diffuse thickening	Normal	Nil	Normal	Slight fibrosis	0	Slight	Marked	Flat, degeneration	+	0	+	Patchy	Patchy	0	Foci	Slight thickening of arteries; mild congestion
Pollak et al. (Case 1)	A	6	Moderate diffuse thickening; "wire loops"	Normal	+	Slight ischemia	Slight thickening	0	Patchy	Marked	Flat, degeneration	+	+	+	Moderate	Patchy	0	Foci	Old hemorrhage; vein occluded by well organized thrombus containing hemosiderin laden macrophages
Pollak et al. (Case 2)	B	½	Mild thickening	Normal	+	Normal	Normal	0	Marked	Nil	Flat	+	0	+	Gross with swelling of connective tissue	Nil	Slight	Occasional	Arteries normal
Pollak et al. (Case 2)	B	3	Diffuse, marked thickening; "wire loops"; narrowing of capillary lumens	Normal	Nil	Ischemia	Very thick and fibrotic	+	Extreme	Nil	Flat	+	0	+	Minimal	Very severe	0	Diffuse	Slight thickening of arteries
Pollak et al. (Case 2)	S	7	Diffuse, marked thickening; "wire loops"	Normal	Nil	Congested	Very thick and fibrotic	+	Extreme	Nil	Flat	+	0	+	Nil	Extreme	0	Diffuse	Thickening of arteries; veins occluded by organizing thrombus

* Histologic analysis of kidneys described in this table was made by the present authors by study of sections of tissue supplied by Professor Vallery-Radot, and Doctors Blainey, Dean, Derow and Moschcowitz.

tention on the lower abdomen and legs (Fig. 5). Phlebograms are contraindicated, lest thrombosis be initiated anew.

Pathologic Features. The pathologic features of the reported cases are listed in Table II, together with those in one of our cases and in one other unreported case.[13] Through the kindness of Professor Vallery-Radot and Drs. Derow, Moschcowitz, Blainey and Dean, we were able to study the histologic sections of their cases in addition to our own. The histologic features of these seven cases are analyzed in Table III. Serial studies were made in our two cases. (Figs. 4 and 8.)

In all but one of the slides studied the glomerular basement membrane was thickened. This thickening was apparent even within fourteen days of the onset of the thrombosis. The thickening was diffuse throughout the glomerulus and in some, resulted in narrowing of the capillary lumens. "Wire-loops" similar to those seen in systemic lupus erythematosus[4] were seen in five of the ten specimens. In systemic lupus erythematosus, however, the thickening of the basement membrane is usually patchy.[3,41] In some cases the glomeruli were congested, in others they were ischemic. Polymorphonuclear leukocytes were observed within the lumens of the glomerular capillaries in three instances. This was possibly the result of slowing of the blood flow through the glomerulus and consequent margination of leukocytes.

The tubules were atrophied in all cases. In those patients in whom onset of the renal vein thrombosis appeared to have been gradual, the atrophy was patchy and of moderate degree; other tubules were dilated. The severe congestion and edema of the kidney probably had spared some nephrons which were functioning until the time of death. In those instances in which the renal vein appeared to have been rapidly occluded, the tubules were markedly atrophic. Protein and casts were found in the tubular lumens. As the tubular epithelium was very flat, it was difficult to detect whether or not the lining cells were degenerated. Fat was found in the cytoplasm of the tubular cells, except in those tubules which were very atrophic. The histologic changes and their progression were similar to the changes observed by Buchwald and Litten[11] in the kidneys of animals after sudden obstruction of the renal vein.

In cases studied ten to fourteen days after rapid occlusion of the renal vein the edema of the interstitial tissue was very striking. In B. B., studied serially, edema was followed by infection and severe interstitial fibrosis which became prominent as the kidney atrophied. In all other cases both edema and fibrosis of the interstitial tissue were noted. The interstitial tissue was infiltrated by chronic inflammatory cells and Bowman's capsules were fibrotic. In several cases the arteries were thickened, the capillaries were congested and there was evidence of thrombosis of veins within the kidney substance.

When the first renal biopsy specimen from B. B. was studied, the histologic features had to be differentiated from those of membranous glomerulonephritis. In both conditions the glomerular basement membrane is thickened and the tubules are degenerated. In membranous glomerulonephritis the glomeruli and tubules are affected to a comparable degree; whereas in renal vein thrombosis the glomeruli are slightly affected, and the damage to tubules and interstitial tissue is disproportionately severe.

The Pathogenesis of the Nephrotic Syndrome in Renal Vein Thrombosis. The development of the nephrotic syndrome in some but not all cases of renal vein thrombosis must be due to a combination of circumstances which allows proteinuria of such degree and persistency that hypoalbuminemia and edema follow. This will be discussed on the basis of the experimental and clinical evidence.

The nephrotic syndrome occurs in diseases affecting the glomeruli and tubules; in some cases, such as lipid nephrosis, it may be associated with tubular damage only. Occlusion of the renal vein and constrictive pericarditis are two conditions in which the nephrotic syndrome apparently develops on the basis of mechanical disturbances. The occurrence of the nephrotic syndrome in a patient with constrictive pericarditis was reported by Blainey, Hardwicke and Whitfield.[6] They suggested that the mechanism of production of the nephrotic syndrome was similar in this case and in their patients with renal vein thrombosis—namely the result of interference with the renal venous return. In their patient with constrictive pericarditis the venous and right auricular pressures were very high (20 mm. Hg). These pressures fell after pericardiectomy. Two months after the operation there was no edema, the urine contained no protein and the levels of plasma protein and serum cholesterol had returned to

normal. Thus when the elevated venous pressure was lowered all features of the nephrotic syndrome disappeared.

In those patients in whom the renal vein was rapidly and completely obstructed, much congestion of the kidney, interstitial edema and tubular atrophy occurred and renal function probably ceased completely within a few days. In this type of occlusion to the renal vein one would not expect the nephrotic syndrome to develop.

If the occlusion is gradual, however, kidney function is maintained and the renal venous pressure rises. This is reflected by a comparable rise in the intrarenal pressure.[36,38,63] The main burden of this increased pressure falls on the peritubular capillaries and on the tubules. Because of the nature of the blood supply of the nephron, through afferent arteriole, glomerulus, efferent arteriole and peritubular capillary, the effects of increased venous pressure on the glomeruli will be considerably less. It should be noted that in the histologic sections there was a striking disparity between the widespread affection of the tubules and the relatively minor changes in the glomerulus.[11] (Table III.) At the same time as there is a rise in the intrarenal pressure, the arterial pressure does not fall but remains constant or rises slightly.[9,56] Hence, glomerular filtration proceeds at a time when the functioning capacity of the tubules is reduced. In such a situation the glomerular filtration rate (C_{Cr}) is maintained or decreased by only 15 per cent.[28,30,56,62] If protein is normally filtered by the glomerulus and reabsorbed by the tubules,[59] much proteinuria will result from the impaired ability of severely damaged tubules to reabsorb the protein normally filtered by the glomeruli.

In patients with renal vein thrombosis protein appears in the urine from the time of onset of the thrombosis; in experimental animals partial ligation of the renal vein is associated with the immediate appearance of protein in the urine. Although all the plasma proteins appear in the urine of patients with the nephrotic syndrome, there is a direct relationship between molecular size of the protein and the quantity of a particular protein in the urine.[24,60,61] Thus the proteins of smaller molecular weight, albumin, alpha-1-globulin and gamma globulin appear in large quantities in the urine and are decreased in the plasma; whereas alpha-2-globulin, beta-globulin, fibrinogen, serum cholinesterase, and cholesterol bound to large protein molecules do not pass through the glomerular filter and are increased in the plasma. The data presented by Vorhaus, Scudamore and Kark[67] and by Squire[60,61] suggest that the rate of synthesis of protein by the liver cell is determined in part by the level of circulating albumin. The loss of albumin in the urine drains the albumin both from the circulation and from the general body pool. This reduction in the normal albumin pool stimulates the hepatic cells to produce more albumin. The serum levels remain low because of the continued outpouring into the urine. The stimulus to the hepatic cell also calls forth a parallel increased production of serum cholinesterase, of molecular size twice that of the albumin molecule. As the serum cholinesterase molecule is too large to pass into the urine, it is retained in the blood and its plasma level is increased in cases of the nephrotic syndrome.[66] When human serum albumin is infused, an elevation in the level of circulating albumin occurs which probably decreases the rate of hepatic synthesis of albumin.[66] The parallel depression in serum cholinesterase production would explain the fall in serum cholinesterase activity observed under these circumstances. The stimulus to the hepatic cell, called forth by the low serum albumin level, may likewise result in increased production of other large proteins of hepatic origin.

The effects of gradual renal vein occlusion are the excretion of albumin in the urine and possibly a decreased urinary sodium excretion. The considerable loss of albumin leads to hypoalbuminemia and to a reduced colloid osmotic pressure.[60,61] These factors, and other consequences of the protein loss, result in the formation of edema.

In experimental animals, Blake et al,[8] Jeanneret[30] and Hwang et al.[28] have shown that a decreased renal clearance of sodium resulted from increasing the pressure in the renal vein. This diminished sodium clearance may persist for as long as seven days after occlusion of the renal vein for twenty to thirty minutes. Although this may be a transient sodium retention, its occurrence at the initial stage of the disease may play a part, although a minor one, in the pathogenesis of edema. Thus on the basis of clinical and experimental observations it is possible to explain many of the features of the nephrotic syndrome in renal vein thrombosis.

SUMMARY

1. Two cases of renal vein thrombosis with the nephrotic syndrome have been observed. One patient died. The second patient had multiple pulmonary infarctions and thrombosis of both common iliac veins. The nephrotic syndrome developed after gradual or incomplete occlusion of the left renal vein. Two months later more rapid occlusion of the right renal vein occurred. The right kidney became functionless, secondarily infected and was later removed. Treatment with anticoagulant and antibiotic drugs reversed the previously relentless downhill course and the patient thereafter made an uninterrupted recovery.

2. The clinical features of the reported cases have been reviewed, and the clinical syndrome of renal vein thrombosis with the nephrotic syndrome has been delineated. In adults, renal vein thrombosis may present with acute symptoms referable to the affected kidney, as the nephrotic syndrome of obscure etiology or as a combination of the two. The presenting picture is related to the rapidity and completeness of occlusion of the vein.

3. In two cases histologic studies have been made on sections from serial percutaneous renal biopsy and autopsy material and in five other cases from autopsy material. The glomerular basement membrane was thickened and the tubules were atrophied. The interstitial tissue was edematous at first and later became the seat of an extensive fibrosis. The changes in the tubules and interstices were out of proportion to the affection of the glomeruli.

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The Effect of Intravenous Administration of Potassium Chloride on Ectopic Rhythms, Ectopic Beats and Disturbances in A-V Conduction*

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POTASSIUM salts have been used in the treatment of cardiac arrhythmias in man since 1930.[1–11] Recent investigations have stressed the beneficial effect of potassium salts in arrhythmias resulting from digitalis toxicity.[7–9] It has been stated that potassium salts selectively abolish the arrhythmias precipitated by digitalis toxicity but have little or no effect on other types of arrhythmias.[8,12] Indeed, potassium salts have been administered to patients with ectopic beats or rhythms in order to ascertain whether or not the abnormal cardiac mechanisms were due to digitalis.[9]

The problem is complicated, however, by the fact that body potassium depletion may itself result in the appearance of ectopic beats which can be promptly abolished by potassium administration.[10,13] Severely diseased hearts, moreover, are reported to be depleted of myocardial potassium[14–19] and this may, *per se*, be a factor in precipitating arrhythmias even in the absence of demonstrable hypopotassemia.

These factors may explain to some degree the beneficial effects of potassium on ectopic beats that have been reported in subjects who were not receiving digitalis.[1,2,4] Thus various factors appear to be important in determining the response of arrhythmias to potassium but the available data do not permit a conclusion as to their relative importance.

The present investigation was designed to evaluate the effect of potassium on arrhythmias which occured in the presence of varying degrees of myocardial disease, in patients who received and in those who did not receive digitalis and in subjects with normal and low serum potassium levels. An incidental observation prompted us to extend our investigation to include the effects of infusion of potassium chloride in ten patients with A-V conduction disturbances.

METHOD AND MATERIALS

Fifty-nine ward and clinic patients of the Philadelphia General Hospital, with various arrhythmias, were treated by intravenous infusion of potassium chloride under continuous electrocardiographic control. Except for three cases in which atrial fibrillation had recently developed, the arrhythmia in all cases had been established for at least twenty-four hours. The arrhythmias were unselected except for the following types which were excluded from study: (1) cases in which long-standing atrial fibrillation was the sole arrhythmia; (2) cases in which the number of ectopic beats was less than 10 per cent of the total; (3) moribund patients; and (4) patients with renal insufficiency and hyperpotassemia.

A careful clinical study which included a complete physical examination was made of each patient; particular attention was paid to digitalis medication and to those factors which might produce potassium depletion. The potassium chloride infusion was pre-

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TABLE I

EFFECT OF INTRAVENOUS POTASSIUM CHLORIDE ON ECTOPIC BEATS*

Patient (case no. and initial)	Heart Disease (grade)	Before K Infusion				K Infusion			After K Infusion				Remarks
		Serum K (in mEq./L.)	Focus Initiating Ventricular Beats (in % of all ventricular beats)			mEq. K for Maximum Effect	Minutes Elapsed to Maximum Effect	Total K Infused (mEq.)	Serum K (in mEq./L.)	Focus Initiating Ventricular Beats (in % of all ventricular beats)			
			Sinus	Supraventricular	Ventricular					Sinus	Supraventricular	Ventricular	
Patients Who Did Not Receive Digitalis													
1, H. B.	I	2.5	82	18a	0	6	10	30	3.3	100	0	0	.....
2, L. S.	I	3.2	76	24a	0	35	40	35	4.9	100	0	0	.....
3, A. P.	0	1.0	0	100a	0	20	15	20	...	100	0	0	Atrial tachycardia with 2:1 block; ventricular rate 90 (cf. Fig. 4.)
4, C. H.	I	2.5	84	0	16v	27	55	47	3.0	100	0	0	.....
5, E. H.	II	3.4	42	18n	12v	24	45	24	...	100	0	0	Order of elimination: v,ne,n; T waves became peaked
6, R. S.	0	2.8	73	22a	5p	30	60	30	3.2	94	6a	0	.....
7, J. H.	0	2.0	85	5a′	10f	60	120	60	3.2	95	5a′	0	.....
8, J. C.	0	3.5	90	10a	0	18	25	42	4.5	100	0	0	.....
9, D. B.	I	5.4	88	12a	0	18	50	18	6.8	100	0	0	.....
10, S. A.	II	4.0	87	13a	0	18	20	18	5.2	100	0	0	.....
11, M. J.	II	4.8	80	20a	0	6	20	12	5.1	100	0	0	.....
12, D. M.	II	5.1	66	34n	0	25	28	25	6.1	100	0	0	Arrhythmia terminated abruptly
13, E. R.	I	4.0	37	63a	0	22	40	30	5.2	100	0	0	Dissociation between sinus and ectopic atrial focus
14, C. T.	+−	4.5	0	100a	0	12	40	29	5.1	100	0	0	.....
15, G. C.	III	4.6	77	0	23v	40	60	40	6.0	100	0	0	Slight peaking of T waves
16, A. F.	I	4.8	67	0	33f	35	60	35	5.4	100	0	0	.....
17, D. W.	+−	4.4	65	0	35f,v	30	40	35	4.7	100	0	0	Order of elimination: f,v
18, B. C.	+−	4.9	57	19a	24p	22	45	22	6.2	100	0	0	Order of elimination: a,p
19, A. B.	III	3.6	55	16a	29v′	40	60	40	4.4	88	0	12v′	.....
20, J. A.	II	3.7	0	79AF	21p,v	25	35	25	5.0	0	100AF	0	Order of elimination: p,v
21, F. T.	I	4.5	13	4a 83AF	0	11	60	16	4.8	91	9a	0	Flutter-fibrillation with sinus runs and atrial beats (cf. Fig. 1.)
22, E. D.	I	5.0	52	48a′	0	16	15	40	6.1	78	22a′	0	Maximal effect with 16 mEq. K; additional K caused slight T wave peaking
23, J. M.	I	4.3	0	100a	0	25	35	25	5.9	0	100a	0	Atrial tachycardia with 2:1 block; ventricular rate 70
24, B. B.	+−	3.6	87	0	13p	22	20	22	4.7	87	0	13p	.....
25, A. J.	I	4.1	67	0	33v′	35	85	35	4.8	67	0	33v′	.....
26, J. J.	III	4.1	0	45AF	55f	40	80	40	...	0	45AF	55f	.....
Patients Who Did Receive Digitalis													
27, H. F.	III	3.1	23	77a	0	25	45	35	4.5	100	0	0	.....
28, C. G.	III	2.6	0	100a	0	20	75	20	2.8	100	0	0	Atrial tachycardia without block; rate 150
29, C. A.	III	3.1	0	100a	0	29	55	29	3.7	0	100a	0	Atrial tachycardia; before K atrial rate 210; after K, 170. 2:1 block unchanged
30, L. D.	III	3.4	65	0	35v	40	45	40	4.4	65	0	35v	.....
31, R. M.	III	3.2	0	95AF	5v	30	90	30	4.3	0	59AF	41v	A-V conduction not altered
32, C. J.	IV	2.9	0	93AF	7f	30	60	30	3.6	0	52AF	48f	A-V conduction not altered
33, J. N.	III	3.3	9	91a′	0	20	40	28	4.3	9	91a	0	Multiple ectopic foci with partial block. Single focus after K (cf. Table III)
34, M. G.	III	...	0	0	100p	18	40	18	...	100	0	0	See Figure 5
35, M. B.	+−	4.1	0	100n	0	6	15	25	4.7	100	0	0	Nodal tachycardia
36, T. D.	III	4.2	0	100a	0	19	30	19	...	100	0	0	Atrial tachycardia with 2:1 block. Ventricular rate 93
37, C. M.	II	4.1	0	100a	0	15	80	15	4.3	100	0	0	Atrial tachycardia with 2:1 block. Ventricular rate 96
38, F. B.	III	4.7	0	100a	0	30	23	30	6.4	100	0	0	Atrial tachycardia without block; ventricular rate 210 (cf. Fig. 6.)
39, J. D.	II	4.3	75	0	25v	15	30	15	4.8	100	0	0	.....

TABLE I (*Continued*)

Patient (case no. and initial)	Heart Disease (grade)	Before K Infusion				K Infusion			After K Infusion				Remarks
		Serum K (in mEq./L.)	Focus Initiating Ventricular Beats (in % of all ventricular beats)			mEq. K for Maximum Effect	Minutes Elapsed to Maximum Effect	Total K Infused (mEq.)	Serum K (in mEq./L.)	Focus Initiating Ventricular Beats (in % of all ventricular beats)			
			Sinus	Supraventricular	Ventricular					Sinus	Supraventricular	Ventricular	
40, W. B.	III	4.7	0	0	100p	12	20	12	4.8	100	0	0	Ventricular tachycardia terminated abruptly
41, J. H.	III	4.5	0	80AF	20p	14	35	14	5.3	0	100AF	0	See Figure 8
42, L. B.	IV	4.2	0	66AF	34f	16	20	21	4.5	0	100AF	0	.....
43, C. C.	IV	4.8	0	66AF	34f,v	25	45	25	...	0	100AF	0	Sudden QRS widening
44, R. H.	IV	4.5	0	55AF	45f	25	30	25	6.0	0	100AF	0	.....
45, B. A.	III	3.8	0	50AF	50f	45	50	45	5.6	0	100AF	0	.....
46, G. C.	IV	4.3	0	100AF	0	23	40	23	4.9	0	100AF	0	AF of 12 hours duration
47, B. H.	III	5.4	0	100AF	0	30	60	30	6.9	0	100AF	0	AF of 16 hours duration
48, J. P.	II	4.1	0	100AF	0	60	60	60	6.9	0	100AF	0	AF of 10 hours duration
49, B. A.	III	4.1	0	50AF	50f	60	120	60	5.1	0	50AF	50f	.....
50, R. B.	IV	4.6	0	70AF	30f	37	50	37	5.2	0	54AF	46f	A-V conduction not altered

* Key to abbreviations:

s: sinus
a: atrial ectopic
AF1: atrial flutter
AF: atrial fibrillation
n: nodal
ne: nodal escape
f: fixed coupling of ventricular ectopic beat
v: varying coupling of ventricular ectopic beats
p: ventricular parasystolic mechanism
': indicates ectopic beats from multiple foci

TABLE II

EFFECT OF POTASSIUM INFUSION ON VARIOUS TYPES OF ARRHYTHMIAS

Type of Arrhythmia	Abolished or Significantly Suppressed	Not Affected or Made Worse	Totals
Ventricular tachycardia....	2	..	2
Ventricular ectopic beats...	16	8	24
Nodal tachycardia....	1	..	1
Nodal ectopic beats.....	2	..	2
Atrial tachycardia....	6	2	8
Atrial ectopic beats.....	14	1	15
Totals...	41	11	52

pared so that it contained 10 mEq. of potassium per 100 ml. of 0.45 per cent saline solution. This was administered at a rate of 0.5 to 1.0 mEq./min., the total amount administered ranged from 6 to 60 mEq. and was given over a period of from 10 to 140 minutes. Preceding the potassium infusion an intravenous solution of 200 ml. of 0.85 per cent saline solution was given over a thirty-minute period. After no demonstrable effect on the electrocardiogram was noted, the infusion of potassium chloride was begun. The injection was discontinued if all ectopic beats were eliminated or if electrocardiographic evidence of potassium toxicity appeared. A dose of 0.5 mEq. of potassium per kilogram of body weight was generally not exceeded unless it was considered that this dose was only partially effective.

When the intravenous infusion resulted in changes, they were directly observed during the period of infusion. Thus a cause and effect relationship could be directly established, and with constant electrocardiographic observation the administration of potassium in this manner is probably safer than the oral route.[9]

Serum potassium levels were determined before and immediately after the infusion. A flame photometer, using an internal standard, was employed for this purpose. In our laboratory serum potassium values in normal subjects have ranged from 3.6 to 5.5 mEq./L.: hypopotassemia was not considered to be present unless a value below 3.6 mEq./L. was obtained.

RESULTS

The effects of potassium administration upon ectopic arrhythmias and upon A-V conduction were studied. The essential data are presented in Tables I and III in which the types of arrhythmias, many of which were multiple, are defined. Potassium was considered effective when the ectopic beats were abolished or signifi-

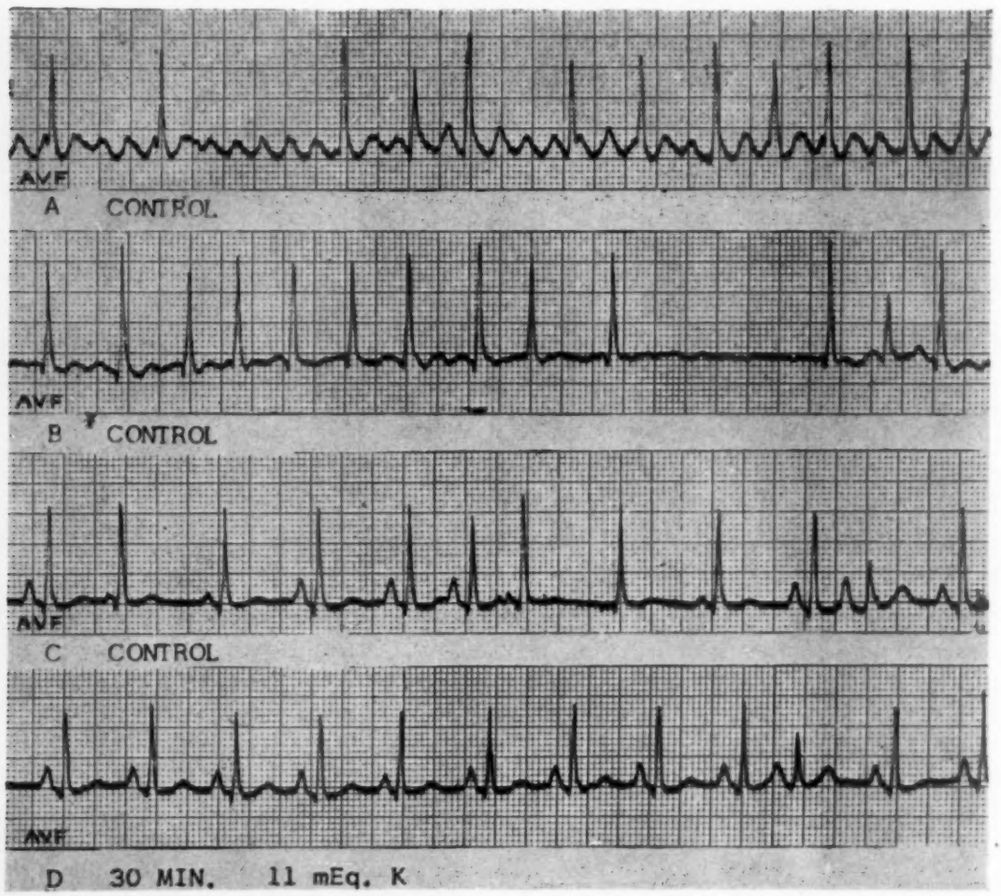

FIG. 1. Case 21, F. T. Electrocardiogram of a malnourished fifty-one year old man with arteriosclerotic heart disease and bronchopneumonia. The patient had never received digitalis. The upper three strips are portions of the control tracing which showed intermittent impure flutter and fibrillation (A and B), alternating with periods of sinus beats associated with frequent ectopic atrial contractions (C). (D) was taken following the infusion of 11 mEq. of potassium at which point the flutter and fibrillation mechanisms had been abolished and the ectopic atrial beats had decreased in number.

cantly decreased. Conversely, potassium was considered ineffective if there was no significant change or if the number of ectopic beats actually increased.

Effect of Potassium Upon the Atrial Mechanism in Atrial Flutter and Fibrillation. There was no detectable change in the atrial mechanism in the five cases of atrial flutter studied, in the twelve cases of established atrial fibrillation and in three cases of paroxysmal fibrillation. An additional patient exhibited intermittent impure flutter and fibrillation with periods of normal sinus beats associated with frequent premature atrial contractions. Infusion of potassium chloride abolished the impure flutter and fibrillation mechanisms and decreased the number of premature atrial beats. (Fig. 1.) In this connection, we have found only three cases recorded in the literature in which potassium (employed in doses larger than those used here) abolished atrial fibrillation. In one case the fibrillation changed to atrial flutter[3] and in the other two, to sinus rhythm.[20,21]

Effect of Potassium Upon Other Supraventricular and Upon Ventricular Ectopic Beats. Forty-seven patients with other supraventricular and ventricular ectopic rhythms are considered in detail in Table 1. For the purpose of considering the effects of potassium upon the group as a whole, the ectopic beats were defined with respect to their site of origin (atrial, nodal or ventricular) and their occurrence in terms of percentage of all beats. For the determination of the latter the percentages of ectopic beats in 200 to 400 con-

secutive electrocardiographic complexes were counted in each case.

The fifty-two arrhythmias presented by the forty-seven patients are listed in Table II and the over-all results are indicated. In thirty-six instances arrhythmias disappeared completely

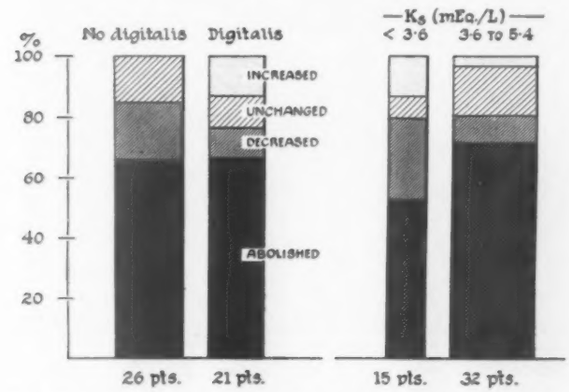

FIG. 2. Comparison of the effects of potassium administration in patients not receiving and in patients receiving digitalis (left half of the figure), and in those with low or normal serum potassium (right half of the figure). The width of the bar graph is proportionate to the number of cases in each category; the height of the variously cross-hatched and stippled areas indicates the percentage of all cases in that particular category, in which ectopic beats were abolished, decreased, unchanged or increased in number.

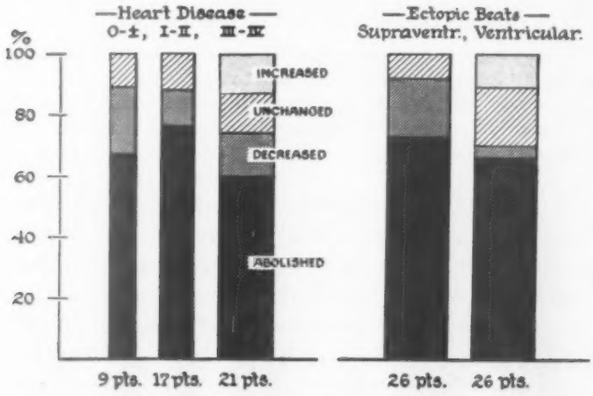

FIG. 3. The effects of potassium administration in patients with no heart disease or varying degrees of heart disease (left half of figure) and upon supraventricular arrhythmias, exclusive of atrial flutter or fibrillation and ventricular arrhythmias (right half of figure). For explanation of symbols, see legend of Figure 2.

following potassium administration and there was a significant decrease in the ectopic beats in five additional cases. In eight instances there was no demonstrable effect and in three cases there was an increase in the number of ectopic beats.

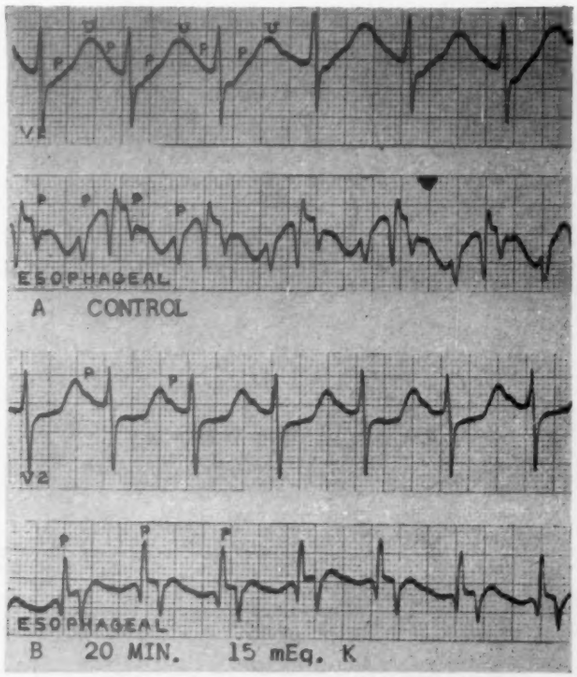

FIG. 4. Case 3, A. P. Electrocardiograms of a thirty-four year old woman, with a clinical diagnosis of epilepsy. There was no underlying heart disease or history of digitalis medication, but the patient had been vomiting perniciously and the serum potassium level was reported to be 1.0 mEq./L. The upper strip of the control tracing shows a hypopotassemic pattern and barely visible P waves. In the esophageal lead the P waves and 2:1 block are more evident. Following 15 mEq. of potassium (lower two strips), the atrial tachycardia with block has disappeared, although with this amount of potassium the hypopotassemic pattern remains.

Thus potassium was effective in abolishing or significantly decreasing the ectopic beats in 79 per cent of the patients with arrhythmias; it was ineffective in 15 per cent and in 6 per cent there was an increase in the number of ectopic beats.

Figures 2 and 3 demonstrate graphically the results of potassium treatment when the forty-seven patients are classified according to the presence or absence of digitalis medication, the presence or absence of a low serum potassium level, the degree of severity of heart disease and the origin of the ectopic beats. It can be seen from these figures that there was no marked difference in the response to potassium in any particular category.

Influence of Digitalis Medication Upon the Effects of Potassium. Potassium abolished or significantly decreased the ectopic beats in twenty-two of the twenty-six patients (85 per cent) who were not

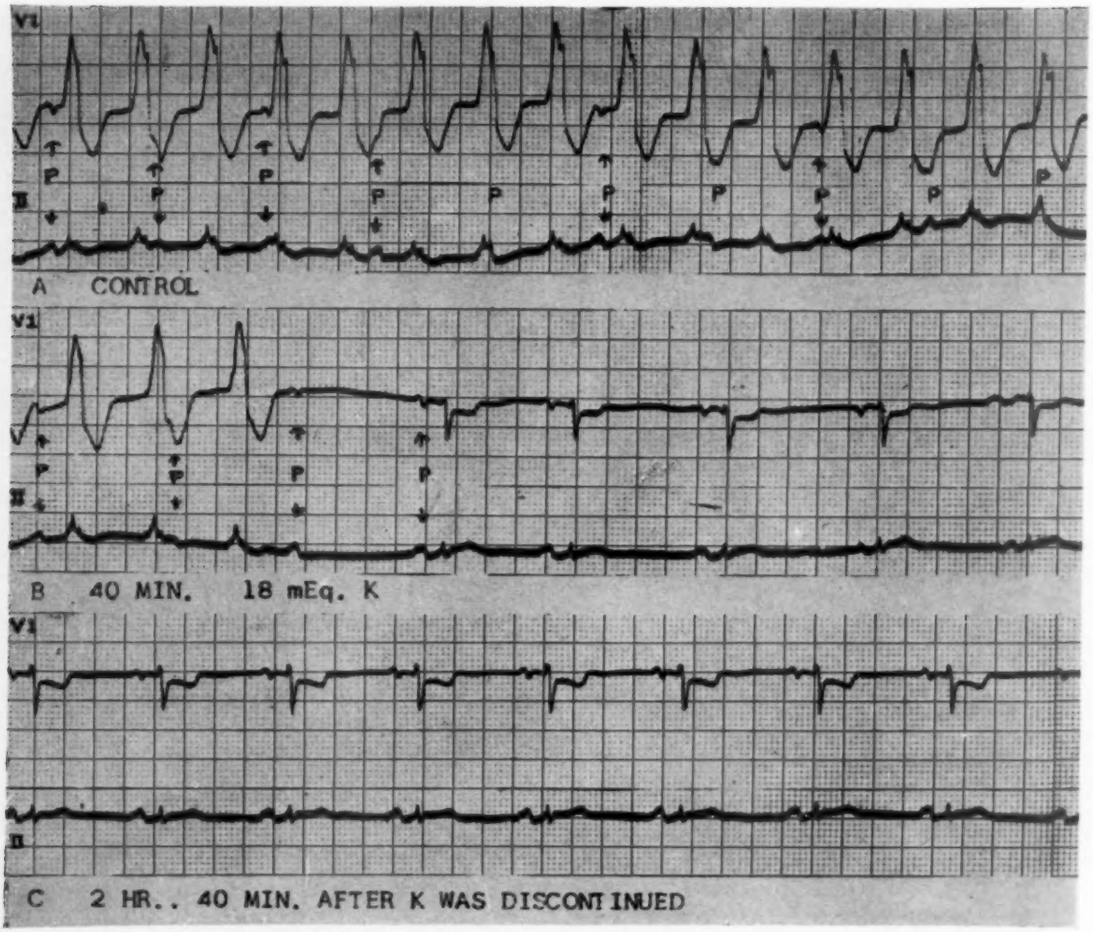

FIG. 5. Case 34, M. G. Electrocardiograms of a seventy-three year old woman with acute myocardial infarction and congestive heart failure. The patient was receiving digitalis. (A) Demonstrates ventricular tachycardia with a rate of 130 per minute. The independent atrial rate was sixty-eight. Tracing (B) was taken at the point of sudden disappearance of the ventricular tachycardia. (C) Was taken two hours and forty minutes later, after potassium was discontinued and shows the persistent sinus rhythm.

receiving digitalis. (Fig. 2.) Potassium had a similar effect on sixteen of twenty-one patients (77 per cent) who were receiving digitalis. The slightly different percentage in the two groups is not statistically significant. The digitalis dosage in three of the twenty-one patients receiving digitalis (Fig. 2) was definitely within the toxic range (Cases 30, L. D.; 41, J. H. and 42, L. B.).

Influence of the Initial Serum Potassium Level on the Effects of Potassium Administration. Potassium significantly decreased or abolished the ectopic beats in twelve of the fifteen patients (80 per cent) in whom preinfusion serum potassium levels were below 3.6 mEq./L. (Fig. 2.) One such patient (Case 3, A. P.), was a thirty-four year old woman who had atrial tachycardia with block in the presence of severe hypopotassemia but without underlying heart disease or history of digitalis medication. (Fig. 4.) Potassium exerted a similar effect in twenty-six of the thirty-two patients (81 per cent) in whom preinfusion serum potassium levels were normal.

Influence of the Severity of Heart Disease on the Effects of Potassium. One group, designated "Heart Disease, None or Possible," consisted of four patients in whom there was no evidence of heart disease and five patients in whom organic heart disease could not definitely be ruled out. Two of the latter had rheumatoid arthritis, one had questionably significant S-T and T changes in the electrocardiogram and two had questionable cardiac enlargement by fluoroscopy. (Fig. 3.) Potassium was effective in significantly decreasing or totally abolishing the ectopic beats in eight of the nine patients (89 per cent) of this group.

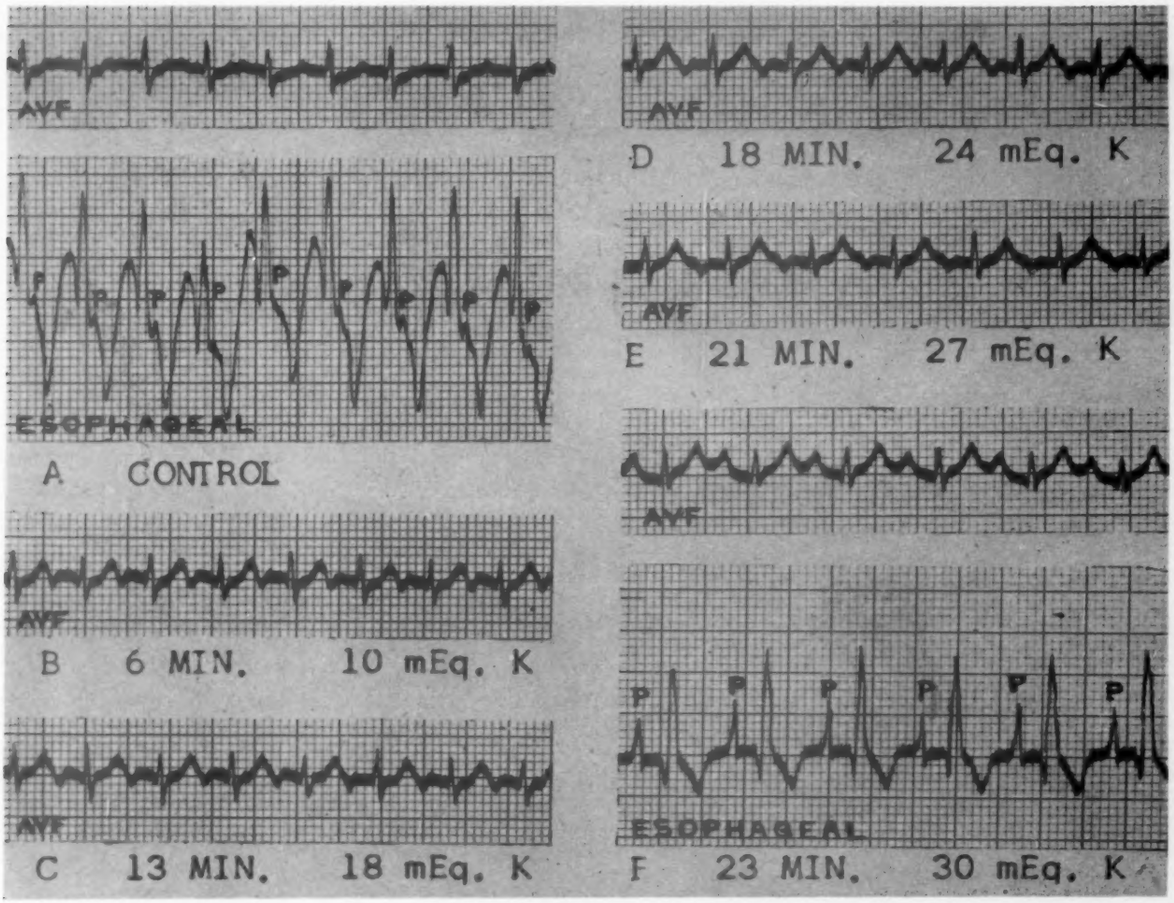

FIG. 6. Case 38, F. M. Electrocardiograms of a seventy-two year old man with cor pulmonale and congestive heart failure. The patient was receiving digitalis. Control tracing (A) shows a supraventric lar tachycardia in which, as the esophageal lead demonstrates, the P waves appear to follow the QRS. (B, C, D and E) demonstrate gradual slowing of the heart rate with the administration of potassium. The P waves are negative. In (E) taken after 30 mEq. of potassium were given in twenty-three minutes, there are upright sinus P waves. The esophageal lead was taken at the same level as in (A).

The group designated "Heart Disease, Grade I–II" included eleven patients in whom there was evidence of heart disease but no history of congestive failure and six patients in whom the single episode of congestive heart failure observed promptly responded to therapy. Potassium was effective in fifteen of the seventeen patients (88 per cent) of this group.

The group designated "Heart Disease, Grade III–IV" included sixteen patients with repeated episodes of congestive heart failure who still responded to routine cardiac management and five patients with clinically "intractable" congestive heart failure. Potassium was effective in fifteen of the twenty-one patients (71 per cent) in this group.

Effect of Potassium Administration Upon Ectopic Beats Arising from Various Foci. When the fifty-two arrhythmias were classified according to supraventricular or ventricular origin, it was found that they were equally divided. Potassium abolished or significantly decreased the ectopic beats in twenty-three (89 per cent) of the supraventricular arrhythmias and in eighteen (68 per cent) of the ventricular arrhythmias. (Fig. 3.)

Manner of Manifestation of the Potassium Effects. In only three of the thirty-three patients responding to potassium did the ectopic beats disappear suddenly; one of these is illustrated in Figure 5. For the most part the ectopic beats disappeared gradually within a period of from ten to forty minutes. The gradual slowing of the rate of an ectopic pacemaker in a case of atrial tachycardia, with ultimate complete suppression, is demonstrated in Figure 6.

Effect of Potassium Infusion Upon A-V Conduction

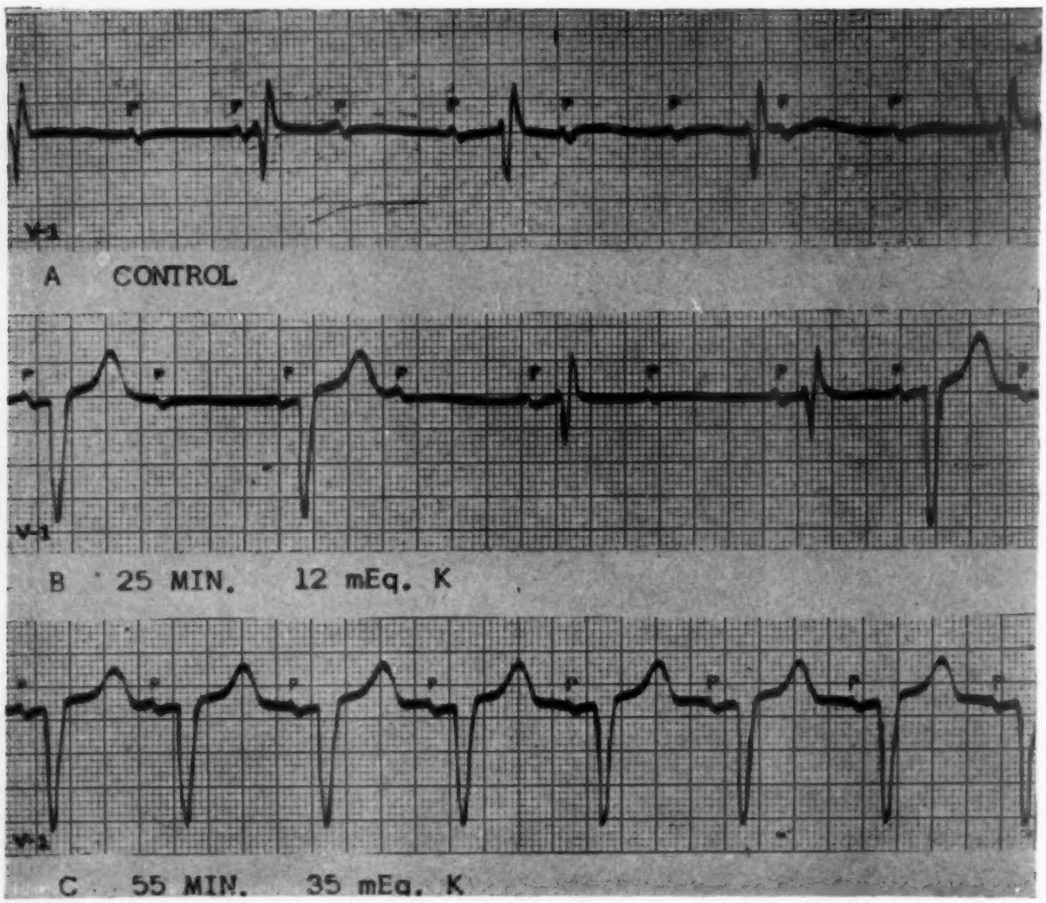

FIG. 7. Case 52, L. O. Electrocardiograms of a sixty-six year old diabetic patient admitted because of a foot lesion. There was no history of heart failure or of medications for heart disease. (A) Shows a run of idioventricular beats with P waves bearing no constant relationship to the QRS complexes. With the infusion of potassium the number of conducted beats increased (B) until there were long runs of 1:1 conductions (C). One hour later the tracing had reverted to its original form.

Disturbances. The effects of potassium on A-V conduction in two patients with complete A-V heart block and eight patients with partial A-V heart block have been tabulated in Table III. Complete A-V heart block present in Cases 55 (M. B.) and 52 (L. O.) disappeared completely. Following cessation of the infusion the rhythm gradually reverted to complete A-V heart block within one-half to one hour. The sequence of events in the second patient is illustrated in Figure 7.

In two of the patients (Cases 33, J. N. and 54 P. D.) who initially manifested partial A-V heart block (one with 67 per cent and the other with 25 per cent of all atrial complexes conducted through the A-V node) the A-V conduction reverted to normal (Table III.) Potassium was ineffective in a third patient, (Case 56 M. B.) with partial A-V heart block of the Wenckebach type.

A fixed degree of A-V heart block in association with atrial flutter was present in the remaining five patients. In two patients (Cases 51, R. C. and 53, H. Y.) the block decreased with administration of potassium and the ventricular rate became faster; in two patients (Cases 57, T. D. and 58, J. M.) it remained unchanged and in one patient (Case 59, M. T.) the degree of block increased from 4:1 to 5:1. In the three patients with atrial flutter in whom the ventricular response was altered by potassium, the changes were of short duration and could be demonstrated repeatedly by stopping and restarting the infusion. In none of these patients was the flutter rate changed.

Thus, contrary to what had been anticipated,

TABLE III

EFFECT OF INTRAVENOUS POTASSIUM CHLORIDE ON ATRIO-VENTRICULAR CONDUCTION*

Patient (case no. and initial)	Heart Disease (grade)	Potassium Infusion: Serum K (mEq. for maximum effect)	Potassium Infusion: Minutes Elapsed (to maximum effect)	Potassium Infusion: Serum K (total mEq. infused)	Serum K (in mEq./L.)	Atrial Complexes: Rate (per minute)	Atrial Complexes: % Conducted (through A-V node)	Ventricular Complexes: Number Conducted (from atrium/min.)	Ventricular Complexes: Escaped Beats (per minute)	Remarks
Patients Who Did Not Receive Digitalis										
51, R. C.	I	9	11	50	Before infusion 4.6 After infusion 6.3	220 AF1 220 AF1	25 33	55 73	0	Change in A-V block could be effected repeatedly by stopping and starting infusion
52, L. O.	I	45	60	60	Before infusion 5.1 After infusion 7.0	75 s 75 s	0 67	0 50	40 0	See Figure 7
Patients Who Did Receive Digitalis										
33, J. N.	III	20	40	28	Before infusion 3.3 After infusion 4.3	10s+98a′ 8s+68a	67 100	72 76	0 0	See Table I
53, H. Y.	II	5	10	30	Before infusion 4.7 After infusion 5.2	300 AF1 300 AF1	27 50	81 150	0 0	Change in A-V block could be effected repeatedly by stopping and starting infusion
54, P. D.	II	5	5	22	Before infusion 4.9 After infusion 5.9	62s 68s	25 100	15 68	18n+47v 0	See text and Figure 9
55, M. B.	IV	29	140	29	Before infusion 3.9 After infusion 4.1	160a 80a	0 100	0 80	44n+50v 0	Ventricular focus first disappeared, then atrial ectopic focus slowed and 1:1 conduction appeared
56, M. B.	III	30	60	60	Before infusion 4.7 After infusion 5.5	100s 100s	90 90	90 90	0 0	Wenckebach periods unaffected by potassium infusion
57, T. D.	III	35	55	55	Before infusion 4.4 After infusion 5.8	350 AF1 350 AF1	30 30	105 105	0 0	.....
58, J. M.	III	33	40	40	Before infusion 4.2 After infusion 4.9	240 AF1 240 AF1	18 18	43 43	0 0	.....
59, M. T.	III	8	12	28	Before infusion 5.8 After infusion ...	250 AF1 250 AF1	27 20	67 51	0 0	Change in A-V block could be effected repeatedly by stopping and starting infusion

* Key to abbreviations:
s: sinus
a: atrial ectopic
AF1: atrial flutter
′: indicates ectopic beats from multiple foci
n: nodal
v: varying coupling of ectopic beats

potassium decreased the degree of A-V heart block in two patients with complete A-V heart block and in two patients with partial A-V heart block with atrial beats of sinus and ectopic origin and in two of five cases of classic atrial flutter associated with fixed grades of A-V heart block.

Effect Upon Other Components of the Electrocardiogram. Except for its effect on ectopic beats and A-V conduction, potassium appeared to have little influence on the other components of the electrocardiogram. The sinus rate remained unchanged in twenty-three patients and became slightly slower in two patients. A slight increase of the T wave amplitude was observed in almost all cases; this was usually more pronounced in patients with low serum potassium levels. Tall, peaked T waves suggestive of hyperpotassemia were seen in only three patients. The QRS duration increased in two cases; these will be considered presently.

Dosage and Duration of Effect of Potassium. The effective dose ranged from 5 to 60 mEq. with an average dose of 23 mEq. The serum potassium levels at the time of disappearance or significant decrease in the arrhythmia were usually 1.0 to 1.5 mEq./L. higher than the levels before potas-

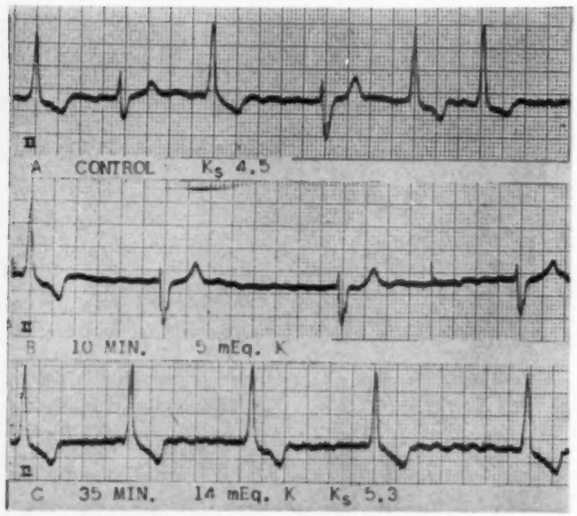

FIG. 8. Case 41, J. H. Electrocardiograms of a fifty-one year old man with rheumatic heart disease and heart failure. The patient was receiving digitalis. The control tracing, (A) demonstrates atrial fibrillation with two ectopic ventricular complexes. After the infusion of only 5 mEq. of potassium the number of impulses conducted through the A-V node was markedly decreased and the rhythm was maintained by an idioventricular focus (B), with slowed infusion of potassium, the ectopic ventricular focus disappeared and all complexes occurred as a result of conduction through the A-V node (C).

sium administration. The effect of potassium did not appear to be related so much to the control serum potassium level as it did to the degree of increase and the speed with which it was produced. The alterations in serum concentration of potassium in the individual cases following infusion are noted in Tables I and III.

There was a wide variation in persistence of the changes in heart rhythm produced by the infusion. In a few patients these changes lasted for only a few minutes or a few hours. In thirty patients the potassium effect persisted for less than twenty-four hours; in eleven patients for more than twenty-four hours. There was no significant difference in the duration of the effects of potassium when compared on the basis of presence or absence of digitalis medication, degree of severity of heart disease, initial levels of serum potassium or site of the ectopic focus.

Untoward and Toxic Effects. When administered with the safeguards used in this study, infusion of potassium salts produced few untoward or toxic effects. If the rate of infusion was more than 0.5 mEq./min., approximately half of the patients complained of a burning sensation along the course of the vein. No other subjective unpleasant effects during potassium infusion were noted.

In three patients (Case 31, R. M.; 32, C. J. and 50, R. B.) with ventricular premature beats increased frequency of the ventricular premature beats developed as a result of potassium infusion. Evidence of severe myocardial damage was noted in this group; digitalis was being administered and in addition two of these patients had a low serum potassium.

In three patients (Cases 5, E. H.; 15, G. C. and 22, E. D.) the infusion was terminated because of the slow development of hyperpotassemic T waves. In another patient with atrial fibrillation (Case 41, J. H.) a very small dose (5 mEq.) of potassium significantly increased the degree of A-V block. This lasted for only a few minutes and disappeared when the rate of infusion was slowed. (Fig. 8.) In addition, in two patients (Cases 43, C. C. and 54, P. D.) it was shown that the typical sequence of electrocardiographic changes which usually occur during potassium intoxication[32] may fail to take place and late electrocardiographic changes may be the first to appear. In both these patients there was a manifestation of significant widening of the QRS complexes without premonitory T wave changes or alteration in the normal atrial mechanism. There was a sudden increase in QRS duration of from 0.10 to 0.14 second after the infusion of 22 mEq. of potassium in one patient (Case 54, P. D.). These changes reverted following the administration of glucose.

COMMENTS

The Interrelationship of Digitalis Medication and the Effect of Potassium Administration. In this study potassium was as effective in abolishing ectopic beats in patients who received digitalis as it was in those who did not. There is ample evidence that digitalis may deplete the cardiac muscle of potassium[22–26] and the antagonistic action of potassium and digitalis has been well documented in animals and human subjects.[27–31] It was not surprising, therefore, that our results paralleled those of previous clinical reports in the finding that potassium was effective in diminishing the ectopic beats of patients who received digitalis. The fact that in this study potassium was similarly effective in suppressing the ectopic beats of patients who did not receive digitalis suggests that factors independent of, or in addition to, digitalis may be involved in the

production of these arrhythmias in patients who did receive digitalis. Some of these factors will now be discussed.

Effect of Potassium Depletion. It is known that a low serum potassium level may be associated with a lowered threshold of excitability of the mammalian heart[32,33] and the occurrence of ectopic beats in patients with hypopotassemia has been frequently observed. An example of this has been shown in Figure 4, the tracing of a thirty-four year old white woman, who had no evidence of underlying heart disease and who was not receiving digitalis, in whom a spontaneous atrial tachycardia with a 2:1 A-V heart block developed in the presence of a serum potassium level of 1.0 mEq./L. Thus the beneficial action of potassium in abolishing those arrhythmias occurring in association with a low serum potassium level, especially in patients free of underlying heart disease, may in great measure depend upon the direct action of potassium in correcting an arrhythmia caused by potassium depletion itself.

Although less than one-third of the cases studied had a lowered serum potassium, the possibility or likelihood of lowered myocardial potassium must also be considered. It is quite likely that many chronic wasting diseases are associated with potassium depletion which may not be reflected in a low serum potassium level,[34] and normal serum levels have been reported to occur despite potassium depletion to the extent of 800 to 900 mEq. in patients with severe chronic heart disease.[35] In the remainder of patients with ectopic beats but without lowered serum potassium one or both of the following conditions which can lower myocardial potassium were present: (1) disease or medication known to result in total body potassium loss, such as vomiting, diarrhea, excessive use of mercurial diuretics or cation exchange resins and steroid hormones; (2) a diseased heart working at or very near the limit of its reserve. There is considerable evidence that appreciable depletion of myocardial potassium may accompany disease and overwork the heart.[14–19]

Analysis of our cases showed that the classification "Heart Disease, Severe" contained the smallest percentage of patients in whom either hypopotassemia or conditions known to cause total body potassium loss were evident. It is possible that the effect of potassium in some of the patients of this group was that of at least temporarily repleting a potassium-deficient and hyperirritable myocardium. The classification "Heart Disease, None or Possible" contained the highest percentage of individuals who had either low serum potassium or conditions known to produce total body potassium loss; the similarity of response in this group may be attributable to a lowered myocardial potassium occurring as a part of total body potassium loss.

Pharmacologic Effect of Potassium. Certain of our observations suggest a pharmacologic effect of potassium as opposed to the physiologic hypothesis predicated herein; both mechanisms have been considered in the literature.[36] Thus in certain cases the number of ectopic beats could be decreased or allowed to increase at will by changing the speed of infusion and in these instances small amounts of potassium administered at a rapid rate had a greater antiarrhythmic effect than larger amounts given at a slower rate. In this connection the findings indicate that the suppression of ectopic beats was associated with a certain increment in the serum potassium level rather than a final absolute level as previously suggested.[3]

Action of Potassium Upon Conduction Disturbances. Relatively few data are available concerning the effect of potassium in altering prolonged A-V conduction time and various degrees of A-V block caused by digitalis. Abolition of A-V heart block by potassium in an animal experiment was attributed to the antagonistic action of potassium and digitalis[36] and it is possible that in two patients the A-V block which was diminished by potassium was a reflection of digitalis action. In another patient who received digitalis, hypopotassemia may have been contributory; shortening of the P-R interval after potassium administration in patients with hypopotassemia has been reported.[13,37]

In two cases neither digitalis nor hypopotassemia were factors. We are not certain as to the mechanism of the potassium effect in these cases but several possibilities present themselves: (1) It has been demonstrated that certain critical concentrations of potassium in the perfusing fluid increase the conduction velocity in the myocardium of the frog,[38] while others decrease it. The action of potassium may then have been that of altering the ionic concentrations toward an optimal level expediting A-V conduction. (2) In certain of our complicated arrhythmias evidences of impaired conductivity and ectopic beats were present simultaneously.

In these cases potassium acted to correct both derangements and to restore a more normal mechanism. These observations suggest that several derangements of myocardial function, such as altered irritability, depressed conduction velocity and possibly impaired contractibility, may appear simultaneously in the presence of potassium imbalance. The beneficial action of potassium in such cases may represent a physiologic effect associated with the correction of the multiple abnormalities and return to a more normal myocardial function.

It is hardly necessary to add that special caution is called for when potassium is used in the presence of impaired A-V conduction because of the possible danger of cardiac arrest due to depression of the ventricular pacemaker, especially with large doses of potassium. As employed in this study, the intravenous administration of potassium proved safe, but the margin between therapeutic and toxic effects may be very narrow. It should also be pointed out that the role of potassium in the abolition of an arrhythmia in any given patient may not be established with certainty unless the initial route of administration is the intravenous one. After the efficacy of potassium has thus been established, more prolonged oral therapy in appropriate doses may be warranted.

SUMMARY

1. Potassium chloride in amounts ranging from 6 to 60 mEq. was administered intravenously to fifty-nine patients with various arrhythmias or disturbances in A-V conduction.

The following arrhythmias, exclusive of atrial flutter and fibrillation, were studied: ventricular tachycardia (two cases), other ventricular arrhythmias (twenty-four cases), nodal tachycardia (one case), atrial tachycardia (eight cases), other supraventricular arrhythmias (seventeen cases). Potassium completely abolished or significantly suppressed the abnormal mechanism in 77 per cent of the arrhythmias, was ineffective in 17 per cent, and in 6 per cent seemed to elicit an increase in the number of ectopic beats. In twenty instances of atrial flutter or fibrillation potassium was almost uniformly ineffective. In six of ten patients with varying grades of A-V heart block, A-V conduction was transiently improved after potassium administration.

2. Potassium was about as effective in abolishing or significantly decreasing the ectopic beats in those arrhythmias which occur in patients not receiving digitalis as in those receiving digitalis. The administration of potassium does not always give information as to whether or not a given arrhythmia is due to digitalis.

3. There was no significant difference in the effect of potassium in patients without heart disease and in those with varying degrees of heart disease.

4. There were no marked differences in the effects of potassium in patients with and without hypopotassemia.

5. The elimination of ectopic beats by potassium was seldom accompanied by other electrocardiographic changes.

6. The general effect and possible mechanisms of potassium action in arrhythmias are discussed.

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Mechanisms of QRS Complex Prolongation in Man*

Right Ventricular Conduction Defects

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THIS is the third of a series of controlled studies of QRS complex deformity syndromes in man.[1,2] The method of study has been to collect cases in which normal QRS complexes can be observed before and/or after the tracing with the QRS abnormality. Thus the patient's own electrocardiogram serves as the control in each case. In the present series the QRS electrical force abnormalities in right ventricular conduction defects are studied.

Controlled studies in clinical electrocardiography have not been possible before because the patterns of the QRS complexes change differently on each of the twelve leads of the conventional tracing when QRS abnormalities appear, and there has been no way to relate the alteration in the QRS complex in one lead with that in another nor has there been a way to compare the changes in all leads of one tracing with the changes in the various leads of another tracing or another patient. As a result, diagnostic criteria of electrocardiography have often been based upon the QRS pattern in only one or two of the leads. For example, the electrocardiographic diagnosis of right bundle branch block is often solely based on the presence of a terminal R wave in precordial lead V_1 and the information contained in all the other leads is ignored.

It is now generally accepted that most body surface leads can be treated as if they were, in effect, recording from the same central electrical force. This makes it possible to integrate the information contained in the QRS complexes of all leads of the clinical tracing into a simple schema of QRS electrical forces or vectors. This makes it possible to calculate semi-quantitatively the changes in QRS electrical forces responsible for the altered patterns of the QRS complexes on all the various leads of a given tracing, and to compare accurately and in detail the information contained in all leads of one tracing with that in all leads of other tracings. This is the method of study used herein; the details have been described previously.[1,2]

MATERIAL

Eighty cases have been collected in which tracings which satisfy currently accepted criteria for the electrocardiographic diagnosis of right bundle branch block were observed: a QRS interval duration of .12 seconds or more with the QRS electrical forces for the last .04 seconds of the QRS interval directed rightward and anteriorly (producing an S wave on lead I and a terminal R-prime at V_1) in the presence of a normal sinus rhythm. In each of these cases there was one or more tracing with normal QRS duration before and/or after the tracing showing the QRS prolongation.) Forty-one or about one-half of the cases were perfectly controlled in that the tracing with normal QRS interval had been recorded after the tracing with QRS prolongation. In all but six of the eighty cases the time interval between the tracing with normal conduction and the tracing with QRS prolongation was less than one year and in none did it exceed two years. Standard and unipolar limb leads and six precordial V leads were recorded in all but eleven of the tracings, and in these eleven the standard limb leads and at least three precordial leads had been recorded. In eight cases CR or CF leads had been used. A normal sinus mechanism was present in all cases, although in four cases there was 2:1 A-V conduction.

An unexpectedly high incidence of what in current electrocardiographic criteria would be called "incomplete right bundle branch block" was encountered among the control tracings in this series, for example, tracings with rightward and anteriorly directed terminal QRS forces but a QRS interval duration of

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only .08 to .11 seconds. Twenty per cent of the control tracings in this series showed such terminal force directions while in the left ventricular conduction defect series reported previously only 4 per cent had this terminal force direction in the control tracing. In a few cases the following transition was seen, first, a normal QRS loop with a duration of .08 seconds, then QRS prolongation to .10 seconds with rightward and anteriorly directed terminal forces of the QRS loop, then QRS prolongation to .12 seconds or more with increased magnitude but little further change in direction of the terminal forces. This sequence must represent different degrees of right ventricular conduction defect. A similar sequence takes place in left ventricular conduction defects with one important difference —the amount of prolongation is usually greater in left ventricular conduction defects and instances of left ventricular conduction defects with QRS interval duration of less than .12 seconds are exceedingly rare,[2] while right ventricular conduction defects of this duration are quite common. In right bundle branch block the QRS interval varies from .12 to .14 seconds in duration in the great majority of cases; QRS durations of .16 were seen in only nine of the eighty cases of this series and in one case the QRS duration was .18 seconds. On the other hand, in left ventricular conduction defects QRS intervals of .16 seconds and more were quite common.

In none of the control tracings of this series was there electrocardiographic evidence of right ventricular hypertrophy. Accordingly, this series sheds no light on the type of QRS complex deformity which the combination of right ventricular hypertrophy and right bundle branch block would produce. However, it does indicate the range of deformity which right bundle branch block may produce in the absence of electrical evidence of right ventricular hypertrophy. It is generally believed that right ventricular hypertrophy will cause the terminal QRS forces in right bundle branch block to be greater than normal in magnitude. In the present series the frontal plane projection of the mean vector for the last .04 seconds of the QRS interval, called the terminal QRS vector, had a magnitude of from 2 to 5 mm. in 90 per cent of the cases and in none exceeded 8 mm.; (in "pattern" nomenclature this means that the largest terminal deflection of the QRS complex in any of the limb leads, whether an S_1 or an R_3 or an R-prime in aVr, never exceeded 8 mm. in amplitude). Similarly the terminal R-prime at V_1 ranged from 4 to 12 mm. in amplitude in 90 per cent of the cases; in one case it was 20 mm. and in another case 23 mm. It can be concluded that the magnitude of the deflection for the last .04 second of the QRS complex must considerably exceed these values in right bundle branch block before the diagnosis of right ventricular hypertrophy plus right bundle branch block can be made. The reason for the wide variation in the amplitude of the R-prime at V_1 in right bundle branch block is not known but may be in part related to variations in body build and thickness of chest wall. It could, to a limited extent, be correlated with the degree of QRS prolongation, for in those cases in which there were longer QRS intervals there was a tendency towards terminal QRS vectors of larger magnitude. No correlation could be found between the magnitude of the terminal QRS vector in a given case and the direction of the mean QRS vector of the control tracing; in other words, the presence of right or left axis deviation in the control tracing did not appear to influence the magnitude of the terminal QRS forces during right bundle branch block.

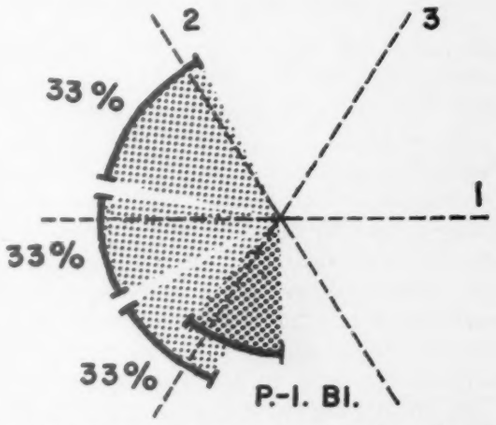


FIG. 1. Distribution of frontal plane directions of terminal QRS electrical forces in 140 cases of right bundle branch block plotted on the triaxial reference figure. The darkly stippled area shows the direction of terminal QRS forces in twenty-one cases of diaphragmatic peri-infarction block.

In the frontal plane the direction of the terminal QRS vector varied through more than one hundred degrees. This is shown in Figure 1; (the eighty cases of the present series were augmented by an additional sixty consecutive cases of right bundle branch block gathered from nearby hospitals for this part of the analysis). It can be seen that in about one-third of the cases the terminal vector is directed rightward and inferiorly, in another third it is directed rightward and horizontally, and in the remaining third of the cases it is directed rightward and superiorly. In general, in cases in which left axis deviation is present prior to right bundle branch block there is a tendency towards superiorly directed terminal vectors when right bundle branch block occurs; while in cases in which there are vertical or rightward axis deviations there is a tendency towards inferiorly directed vectors when right bundle branch block occurs. This is the reverse of what one would expect if axis deviation were due to a shift of the anatomic axis of the heart and the explanation for this phenomenon is not known.

No attempt was made to study the effects of right

bundle branch block on the T waves or on the ventricular gradient. Similarly it was not possible to make clinical or pathologic correlations in these cases for this information was not conveniently available in most instances.

THE NATURE AND SITE OF THE CONDUCTION DEFECT IN RIGHT BUNDLE BRANCH BLOCK

An important feature of experimental right bundle branch block is the change in the first part of the QRS complex which takes place in all leads when the block is produced; this can be seen in every published example of experimental right bundle branch block.[3–8] This means that the way in which excitation enters the ventricles is altered in experimental right bundle branch block. What occurs in clinical right bundle branch block is quite different. In the present series there were six cases in which myocardial infarction occurred at the time right bundle branch block developed and in these cases the initial parts of the QRS complexes in the various leads were changed at the onset of the block (in three of these cases there was subsequently unblocking without further change in initial QRS forces, proving that the deformity of the initial part of the QRS complexes was due to the infarction in these instances). However, in none of the remaining seventy-three cases was there any change of the initial part of the QRS complexes on any lead with the development of right bundle branch block; the cases in Figure 2 illustrate this. In other words, excitation enters the ventricles normally in clinical right bundle branch block and this represents a fundamental difference between clinical and experimental right bundle branch block.

That the initial part of the QRS loop is spared in clinical right bundle branch block has been noted before,[9–13] but its significance for an understanding of the mechanism of right bundle branch block and the difference between clinical and experimental right bundle branch block in this regard have not been previously recognized. It has been suggested that if normally the first part of the ventricles to become excited were the left side of the interventricular septum via the left bundle branch, one would not expect the initial QRS forces to be altered in right bundle branch block.[11] However, the fact that initial QRS forces are altered in experimental right bundle branch block must be considered evidence against the possibility that the left side of the interventricular septum alone accounts for the first QRS electrical forces. Furthermore, it is likely that this initial activation of the left side of the septum, if it takes place at all, produces an extremely small and brief electrical force and may be too small to be recorded in human body surface leads.[14,15] The portion of the QRS interval that is spared with the development of right bundle branch block is far too great to be explained on such a basis. In the cases of the present series it was observed that from 50 to 80 per cent of each QRS complex in the limb leads of the control tracing was unaltered by the development of right bundle branch block. This means that the first .04 to .06 second of the QRS interval as recorded in the limb leads is unaltered by right bundle branch block, which is certainly a larger portion of the QRS interval than can be attributed to septal activation. A somewhat shorter portion of the QRS complex was unaltered in precordial leads V_1 and V_2; this point will be discussed further.

There are other possible explanations for this sparing of the first part of the QRS interval with the development of right bundle branch block. (1) Perhaps the electrical forces generated by the right ventricle during this first .04 second of the QRS interval are too small to be recorded in body surface leads. However, if this were the case, the P-R interval should become prolonged by .04 to .06 seconds whenever left bundle branch block takes place. The P-R interval before and during left bundle branch block was studied in the group of cases of left ventricular conduction defects reported previously and no consistent change was found. It can be concluded that this is not the explanation for the QRS sparing effect seen in right bundle branch block.

(2) If the first QRS forces to be generated from the right ventricle have essentially the same direction as the first forces from the ventricles as a whole, there would be no change in the direction of initial QRS forces with the development of right bundle branch block. However, it is unlikely that they could have exactly the same direction as the first QRS forces of the ventricles as a whole in all cases. Even if this were the case, there should be a reduction in the amplitude of the initial QRS forces with right bundle branch block. However, in none of the cases did this take place and therefore this too cannot be the explanation.

(3) The only remaining, and from many points of view the most probable explanation, is that in clinical right bundle branch block the

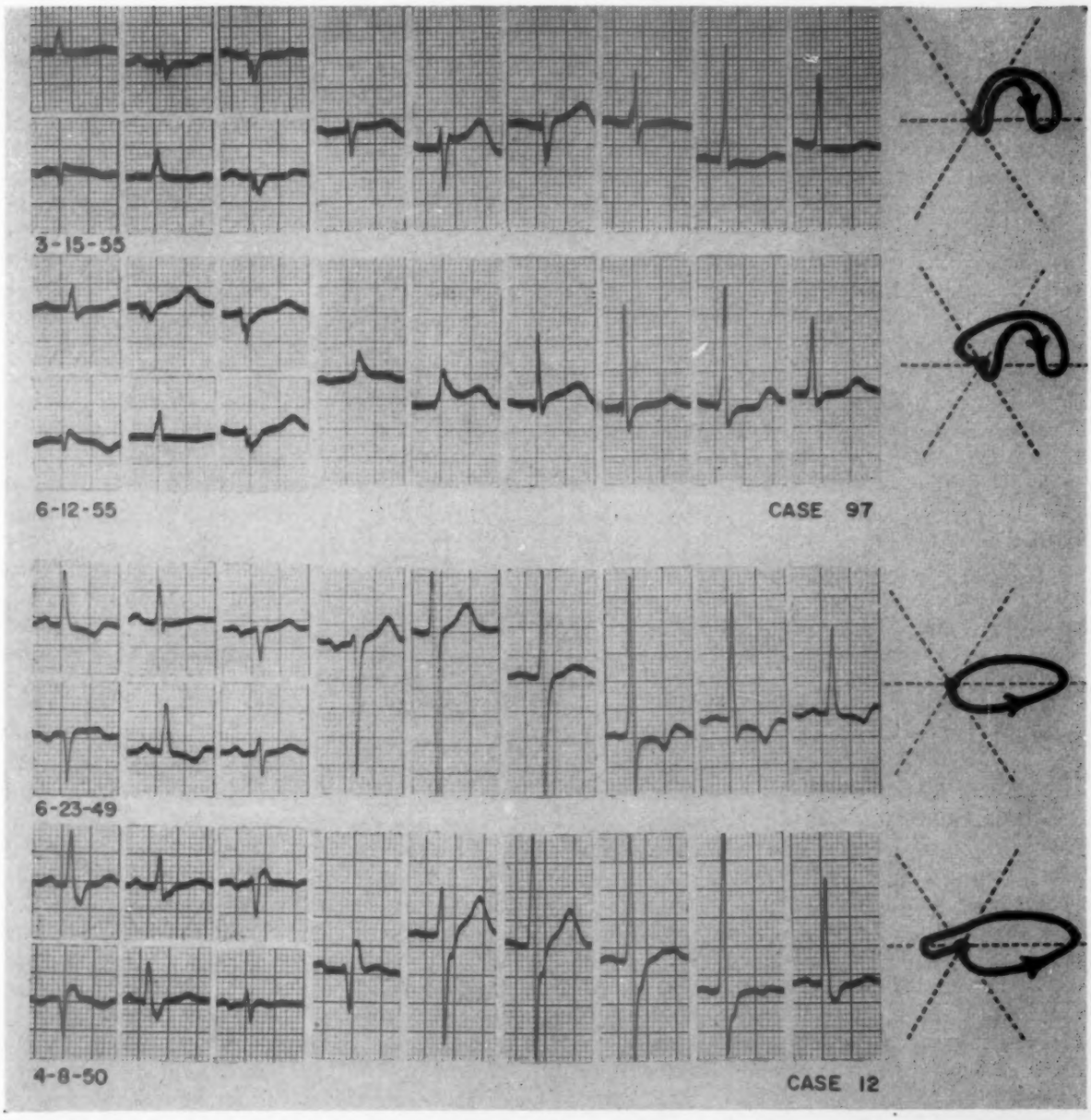


FIG. 2. Two cases of right bundle branch block with control tracings. The small tracings on the left are the limb leads; the standard limb leads above and the unipolar limb leads, R, L and F below. The large tracings are precordial leads V_1 through V_6. In this and all subsequent figures, frontal plane projections of QRS loops are shown, constructed from the limb lead tracings. Case 97 is an example of diaphragmatic infarction which had been followed for several months (the Q_2, Q_3 and Q_f show evidence of "healing") with development of right bundle branch block shown in the lower tracing. Note that the first .04 second of the QRS complex in the limb leads is unchanged by the development of the block, while only the first .02 second of the QRS complex at V_1 and V_2 is spared. Case 12 is an example of right bundle branch block developing in a patient with left axis deviation. Note that there is no deformity of the QRS loop up to the instant the abnormal right ventricular forces are generated.

"lesion" lies more distally along the conduction pathways of the right ventricle than it does in experimental right bundle branch block. In this explanation the portion of the right ventricle which normally is activated during the first .04 to .06 second of the QRS interval is not included in the blocked area and, therefore, the deformity of the QRS complex in right bundle branch block does not involve the first .04 to .06 second of the QRS interval. This would mean that

clinical right bundle branch block is not "complete right bundle branch block," if this term signifies that all regions of the right ventricle are included in the blocked area and all branches of the right bundle are blocked.

Such an hypothesis would be strengthened if cases of clinical right bundle branch block could be found in which the initial QRS force changes and other features of experimental right bundle branch block were present. These cases could then be attributed to lesions higher in the right ventricular conduction system than those seen in conventional clinical right bundle branch block. No such cases were encountered in the present series, but five cases have been collected from the literature in which there are certain properties resembling experimental right bundle branch block.[16–20] First in all five cases there was 2:1 A-V conduction and shifting types of bundle branch block—right, left and bilateral bundle branch block—indicating that the lesion lay near the bifurcation of the bundle of His. In the cases in which there was alternating right and left bundle branch block the P-R interval was different during left bundle branch block than it was during right bundle branch block, indicating that during the right bundle branch block phase all regions of the right ventricle and all branches of the right bundle had been blocked. Second, while in only two of these cases were tracings obtained with QRS complexes of normal duration (perhaps representing normal ventricular conduction), in both cases the direction of initial QRS forces was different during normal ventricular conduction than it was during right bundle branch block. These are the only two cases of clinical right bundle branch block observed in which initial QRS forces were changed in direction when uncomplicated right bundle branch block developed. The third feature is the unusual contour of the QRS complex during right bundle branch block in many of these cases. The QRS forces generated during the last .04 second of the QRS interval (the terminal QRS forces) are much larger than in conventional right bundle branch block giving leads II and III much taller terminal R waves than are ordinarily seen. This type of QRS complex is characteristic of experimental right bundle branch block and the QRS complexes in these cases look much more like those of experimental right bundle branch block than clinical right bundle branch block. Perhaps the increased magnitude of the terminal QRS vectors in these cases and in experimental right bundle branch block is due to the fact that a relatively larger area of right ventricle is included in the blocked area. Certain features of these five cases can be seen in Figure 3 in which relevant tracings from two of the cases are reproduced from the literature.

This type of controlled study sheds light upon other aspects of the electrical defect in right bundle branch block. It has long been held that in bundle branch block there is simply a change in the sequence in which various regions of the ventricles undergo activation with the region distal to the block delayed in becoming activated. As shown previously, if this were the case the QRS complexes in bundle branch block would be prolonged but should show no change in the net enclosed area.[2] Since in both left and right bundle branch block the net enclosed areas of the QRS complexes on the various leads are greatly increased, these conduction defects cannot be due to simply an alteration in the timing of activation of the various regions of the heart but must also involve significantly abnormal methods of spread of activation in the regions of the heart distal to the block.

This is perhaps better seen in right bundle branch block than in left bundle branch block. When the tracing with block is compared with the control tracing, (Case 12, Figure 2), it appears as if an extraneous potential generated toward the end of the QRS interval were simply added as a sort of appendage to the normal QRS complex during right bundle branch block. The extra deflection is always simple and monophasic in contour and is due to an electrical force directed anteriorly and rightward, as if from the free wall of the right ventricle. It is generally believed that in right bundle branch block there is a delay or arresting of right ventricular activation when excitation reaches the site of the block. However, if this were the case, one would expect left ventricular forces to dominate the writing of the QRS complex during this delay and before the blocked region of the right ventricle is depolarized. When the tracing with right bundle branch block is compared with its control, it can be seen that there is no such deformity of the QRS complex immediately before this abnormal right ventricular force is generated. Therefore, as soon as excitation reaches the site of the block it immediately spreads out into the surrounding regions of the right ventricle, as if the lesion were a "leak" for excitation rather than a delaying or

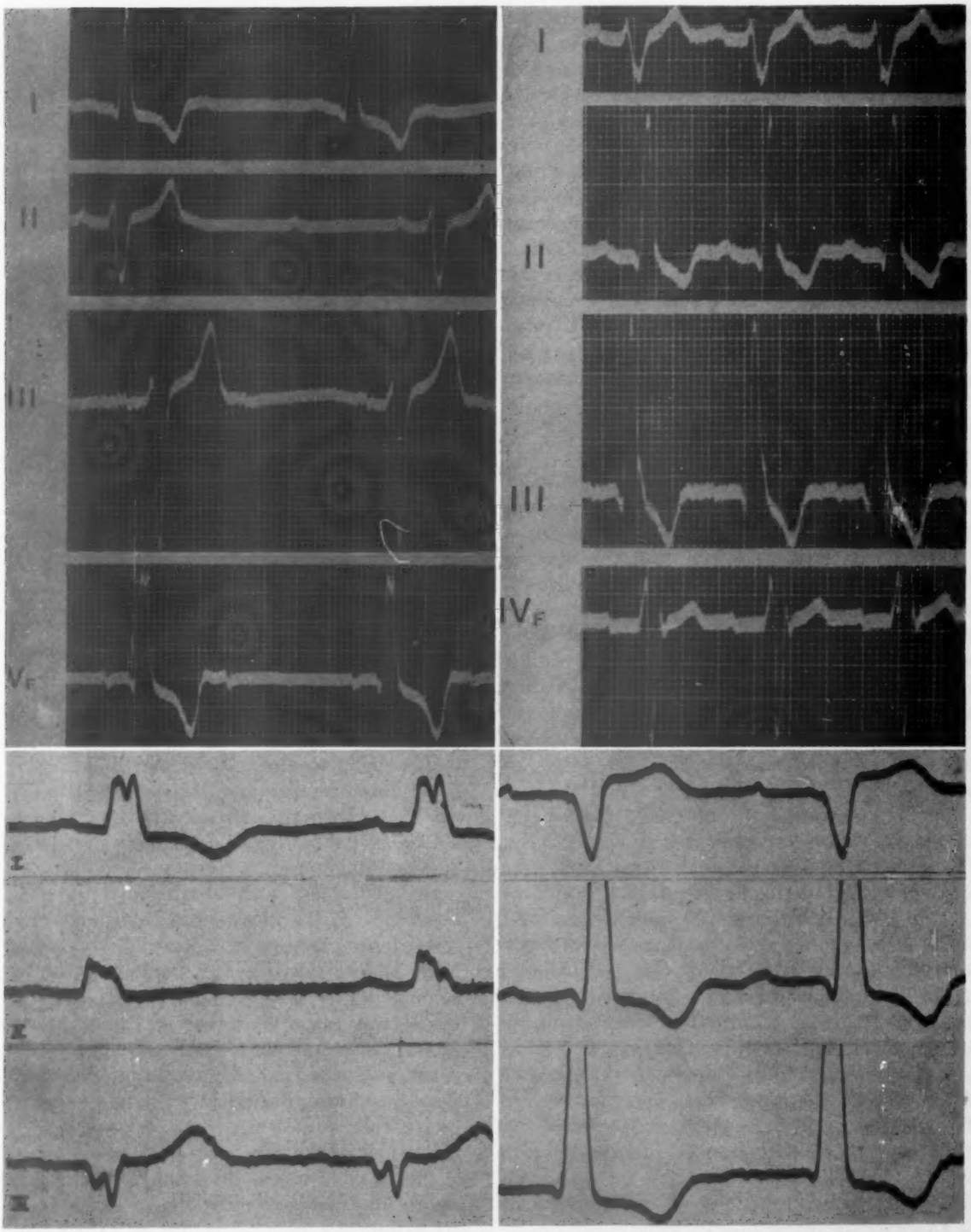


FIG. 3. Unusual deformity of the QRS complex of the right bundle branch block type. Note how large the terminal QRS forces are during the block as shown in the tracing on the right for each case. Note also that in the upper example, the P-R interval is .04 second longer during right bundle branch block. Both cases are reproduced from the literature, the upper from Dressler[17] and the lower from Straus and Langendorf.[16]

blocking mechanism. The remainder of the right ventricle is depolarized by abnormal routes and slower than normal velocities. Probably intramyocardial spread of activation takes place for conduction is slower by this route than by the Purkinje fiber network.

Too little is known about the electrophysiologic properties of the right ventricle and the ventricular conduction system in man to warrant speculation regarding the exact site or nature of the block in right bundle branch block. In recent years there have been reports of careful histologic examination of the right bundle in human beings with right bundle branch block with no abnormality found.[21] However, only the proximal part of the right bundle was studied in these cases and that may be the reason why no abnormality was found. Since in some cases of right bundle branch block the QRS complex of the limb leads is spared for the first .04 second while in others it may be spared for as much as .06 to .07 second, it is possible that in some cases the lesion is more distal in the right bundle system than in others. However, it is difficult to make this measurement accurately from the conventional clinical tracing and is no doubt influenced by such factors as the relative distance of the electrode from various parts of the heart and by different degrees of attenuation of the electrical events of the heart by differences in body build, among other factors.

The observation that the initial .04 to .06 second of the QRS loop is spared with the development of right bundle branch block is of importance in practical clinical electrocardiography, for it means that the direction of the mean vector plotted from the first .04 second of the QRS interval is the same with and without right bundle branch block. For example, one can determine whether a patient with right bundle branch block had a right or left axis deviation prior to the right bundle branch block by examining the axis deviation represented by the first .04 to .06 second of the QRS complexes in the limb leads of the tracing with right bundle branch block. By the same token, the deformity of the initial part of the QRS complex produced by myocardial infarction should be easily identified in the limb leads in the presence of right bundle branch block.

It was noted earlier that the QRS-sparing effect seen in right bundle branch block is more striking in the limb leads than it is in the precordial leads. For example, while the initial 50 to 80 per cent of the QRS complexes are spared in the limb leads of the control tracing when right bundle branch block appears, only the first 25 to 50 per cent of the QRS complexes at V_1 and V_2 are spared. The reason for this must be that the earliest forces generated from the right ventricle are too small to be recorded in the relatively more remote limb leads but can be picked up in the more proximal V_1 and V_2 precordial leads. These forces must be generated from an extremely anterior region of the right ventricle because they cannot be recognized in the other precordial leads. Because they are recorded at V_1 and V_2 as positive components of the QRS complex, they must be anteriorly directed. This latter point is important because it means that in right bundle branch block the QRS complex at V_1 and V_2 may be positive for the first .04 second. An initial R wave at V_1 of more than .04 second duration in the presence of a normal QRS interval duration is often diagnostic of strictly posterior myocardial infarction.[1] However, this is not true in the presence of right bundle branch block and this is the only type of QRS complex deformity due to myocardial infarction which is obscured by right bundle block.

It is of interest that when incomplete right bundle branch block extends to complete right bundle branch block the additional prolongation is superimposed later during the QRS interval than when the control tracing is normal. This suggests that the lesion in the right ventricular conduction system has the same location in both incomplete and complete right bundle branch block. It may be that the QRS complex is shorter in duration in incomplete right bundle branch block than it is in complete right bundle branch block due to, among other factors, (1) fewer fibers of the right bundle are involved, and, therefore a smaller portion of the right ventricle is blocked or (2) excitation may regain passage in the Purkinje network beyond the block; this would accelerate conduction to the remainder of the right ventricle.

In vector electrocardiography there is a basic assumption that all body surface leads are recording, in effect, from the same central electrical forces. The demonstration that there is a brief period in the course of writing the QRS complex in right bundle branch block when the precordial leads record electrical forces that cannot be identified in limb leads, is proof that this assumption is not always correct. How-

ever, this demonstration of "isolated" QRS positivity ("isolated" in that these are potentials which can be recorded in certain of the conventional body surface leads but not in others) is the first and, so far, only exception to this assumption that has been demonstrated for QRS forces. A similar, but equally infrequent exception for T forces, "isolated T-negativity" has also been described.[22] These exceptions do not invalidate the vector concept but simply indicate that, as in all technics which attempt to simplify and schematize an intrinsically complex phenomenon, there are bound to be instances when the observations do not fit into the simple schema. Under these circumstances a more complex schema is necessary to explain the findings. Clinical electrocardiography is fortunate that such exceptions are rare and, so far, of little importance in diagnostic clinical electrocardiography. This discrepancy between limb leads and precordial leads in right bundle branch block perhaps partly explains why the information contained in the cathode tube QRS loop (which is recorded from relatively remote electrode locations) does not always agree with the information contained in the precordial QRS complexes in a given case of right bundle branch block. In addition it indicates how cautious one must be in relating information obtained from extremely proximal leads, such as intracavitary and intramural leads, to the information contained in the relatively more remote leads of the conventional clinical tracing.

MYOCARDIAL INFARCTION AND RIGHT BUNDLE BRANCH BLOCK

In thirty-nine or nearly one-half of the eighty cases of this series, QRS complex deformity of myocardial infarction was present in the control tracing. Most of the remaining cases were in an older age group and, although the clinical background of these cases was not known, it is likely that coronary artery disease was present in many. Thus coronary artery disease is the most common cause of acquired right and left ventricular conduction defects.

In five of the thirty-nine cases, the direction of the abnormal initial QRS forces changed with the development of right bundle branch block indicating that the electrical location of the infarction shifted at the time of onset of the block. In two of these five cases there was a subsequent unblocking with no further change of the initial QRS forces, proving that infarction and not right bundle branch block caused the change in initial QRS forces in these cases. In none of the other cases was the initial QRS complex deformity of infarction changed by the development of right bundle branch block. Thus the "Q waves" of infarction can be identified even in the presence of right bundle branch block and the Q wave criteria for the diagnosis of infarction are the same with or without this block.

In eighteen or nearly one-half of the thirty-nine cases of myocardial infarction with right bundle branch block the QRS complex deformity of diaphragmatic infarction was seen while the remaining cases were equally divided among anterolateral, strictly anterior and strictly posterior electrical locations of the infarct. This differs from the distribution of infarct locations in the cases of left ventricular conduction defects with infarction in which there was an anterolateral electrical location of the infarct in more than one-half of the cases and diaphragmatic infarction in only one-third.

Two factors may play a part in the predisposition of diaphragmatic infarction to develop right bundle branch block. First, while the specific arterial supply of the right bundle is not known in man, the right ventricle, and therefore the major portion of the right ventricular conduction network, is principally irrigated by the right coronary artery. This is the artery which, when occluded, accounts for most cases of diaphragmatic infarction.

A second factor may be peri-infarction block, which has been described in detail previously.[1,2] In this syndrome the terminal QRS electrical forces are altered in direction by infarction becoming opposite in direction to the initial QRS forces which are responsible for the Q waves. The mechanism of peri-infarction block is believed to be as follows: the subendocardial location of the infarct delays the spread of excitation to the epicardial regions of the myocardium which overlie the infarct, consequently, the last QRS forces to be generated during the QRS cycle are those from the epicardial layers overlying the infarct.

This type of block is usually associated with little or no prolongation of the QRS interval. However, in certain cases, depending perhaps upon the size of the infarct and secondary changes in the adjacent myocardium, the QRS interval may be prolonged to .12 second or more. Under these circumstances the QRS complexes on the various leads will resemble those

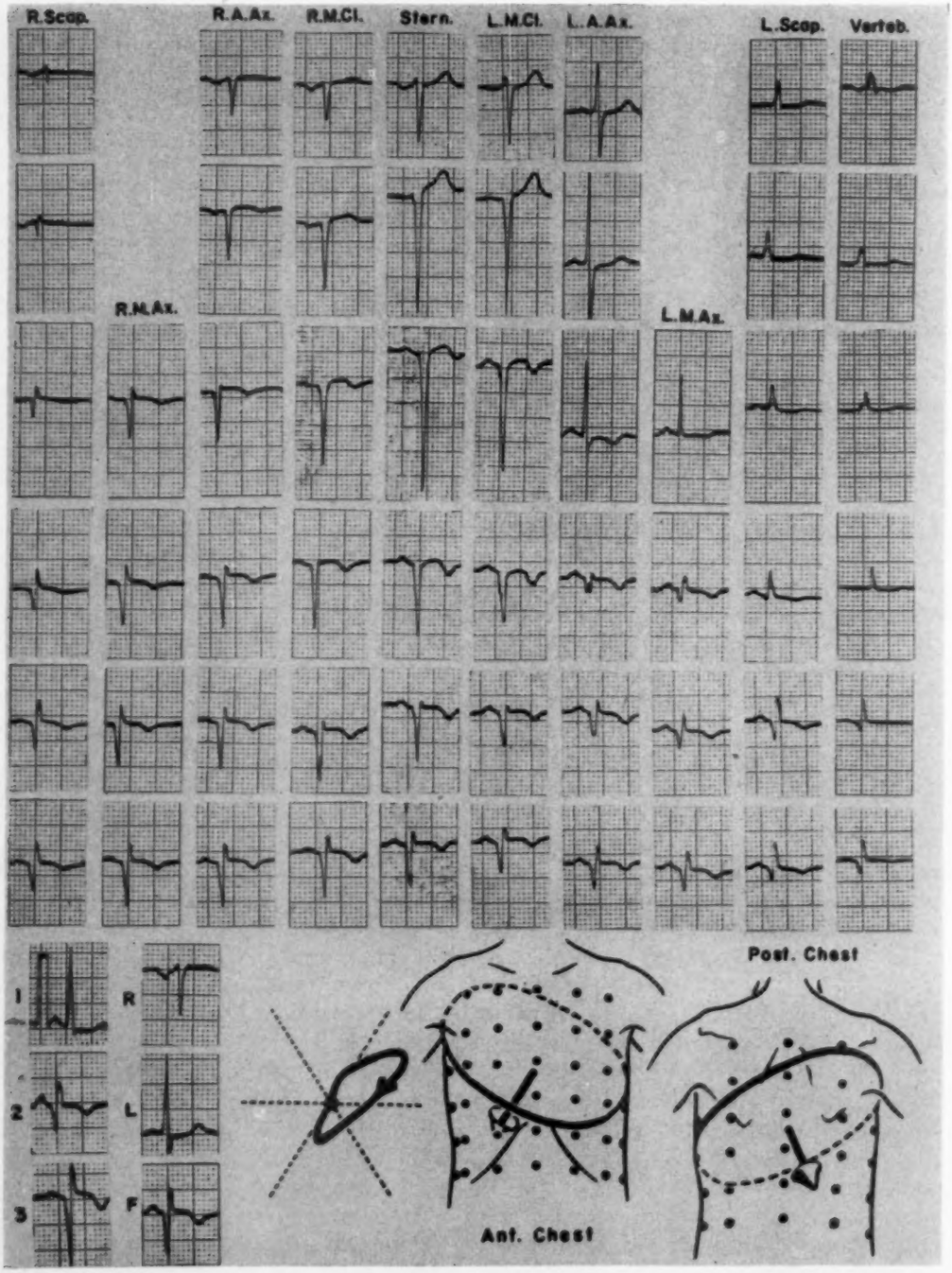


FIG. 4. Direction of the terminal .02 second QRS vector, using the null contour method as described in the text, in a case of diaphragmatic infarction with peri-infarction block. Limb leads are shown at the lower left. The black dots in the two figures at lower right indicate the locations on the body of the electrode positions where the tracings were recorded. The circumferential line, the null contour, indicates the distribution of relative zero potential on the chest for the last .02 second of the QRS interval. It can be seen that the area of positivity for this vector (the region on the chest where terminal R-prime deflections are recorded) occupies the lower part of the chest, extending somewhat higher anteriorly on the right than on the left side of the chest.

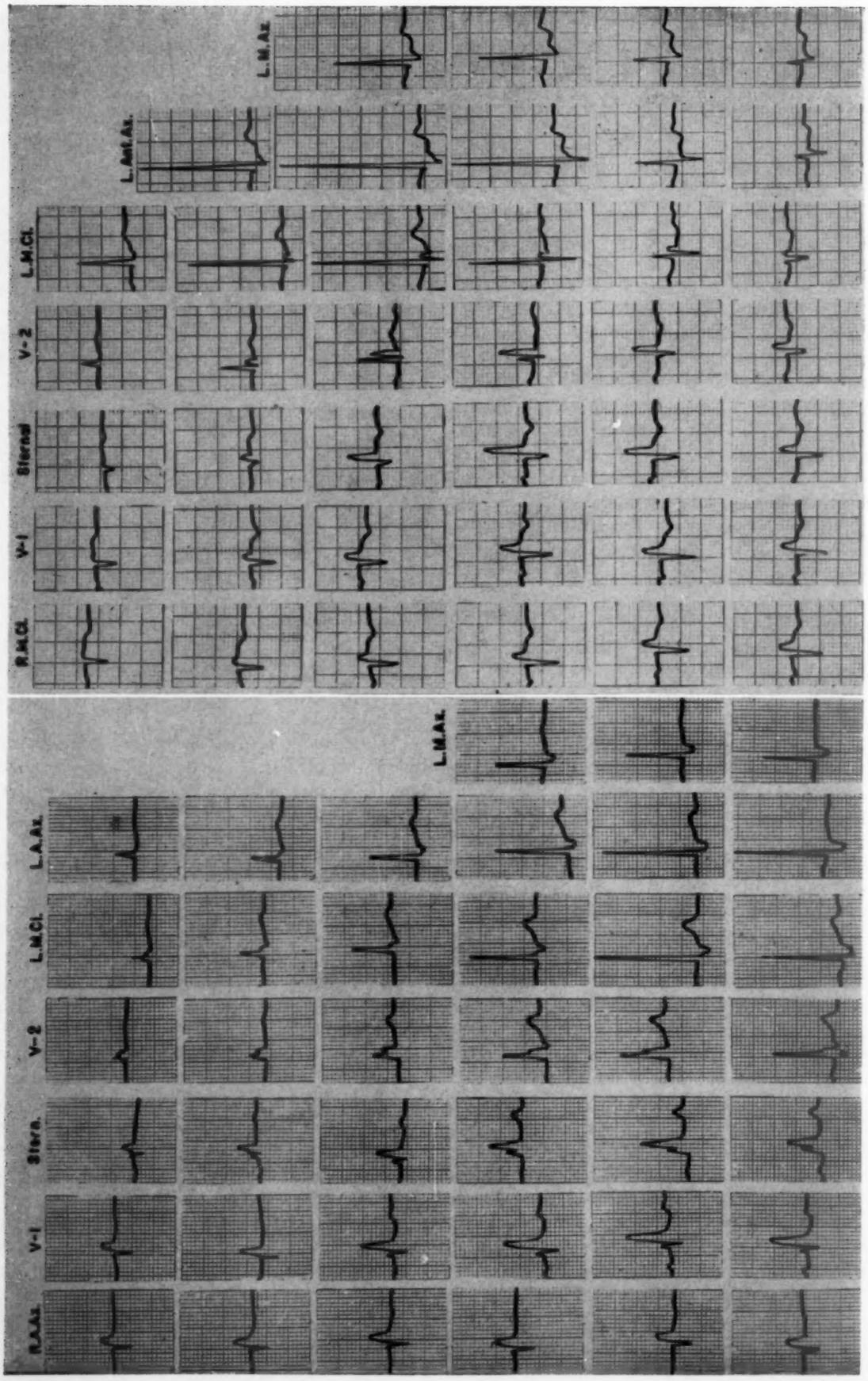
of bundle branch block. For example, in peri-infarction block associated with anterolateral infarction the terminal forces are directed leftward and superiorly. This is the same direction that terminal QRS forces have in left bundle branch block and therefore the QRS complexes in anterolateral peri-infarction block with QRS prolongation often closely resemble those of left bundle branch block.[2] On the other hand, in peri-infarction block of diaphragmatic infarction, the terminal forces are directed rightward and inferiorly, opposite to the direction of the initial QRS forces responsible for the Q_2 and Q_3 and Q_f of diaphragmatic infarction. This terminal force direction produces a terminal S wave on lead I, and when associated with QRS prolongation of .12 second or more, the lead I QRS complex closely resembles that of right bundle branch block. It is possible, then, that certain cases called diaphragmatic infarction with right bundle branch block are actually examples of diaphragmatic infarction with peri-infarction block; this might partially account for the high incidence of QRS prolongation resembling right bundle branch block among cases of diaphragmatic infarction.

The differentiation of diaphragmatic peri-infarction block from right bundle branch block is important in clinical electrocardiography because, as will be seen, it is possible that the terminal force abnormality of peri-infarction block can occur in the absence of Q waves diagnostic of infarction. Therefore an attempt was made to study the difference in terminal QRS force abnormality in the two syndromes more accurately than can be done from the twelve-lead clinical tracing. The method selected was the null contour method, which is the most accurate method so far devised for determining the directions of instantaneous vectors from body surface electrode locations. In this method V lead QRS complexes are recorded from a large number of systematically selected electrode locations on the surface of the chest. The electrode locations in which the QRS complex writes a null or zero component for the electrical force under study are identified; these electrode locations form a pathway around the chest defining a plane to which the electrical force is perpendicular. By plotting such planes (or null contours, as the physicist calls them) for the electrical force under study, it is possible to define the spatial direction of the force with reasonable precision.

Using this method, the spatial direction of a mean vector for the last .04 second of the QRS interval was determined in twelve cases of right bundle branch block and twenty-one cases of diaphragmatic infarction, in sixteen there was a peri-infarction block with only slight prolongation of the QRS interval. The findings in a typical case of diaphragmatic peri-infarction block are shown in Figure 4 and two cases of right bundle branch block are shown in Figure 5. It can be seen that while the mean terminal force is rightward in both syndromes it is as much as ninety degrees more anteriorly directed in right bundle branch block than in diaphragmatic peri-infarction block. From a "pattern" point of view, in right bundle branch block the terminal QRS force is sufficiently anteriorly directed to cause V_1 and V_2 to lie in its area of positivity; as a result terminal positive deflections (R-prime deflections) are recorded in the QRS complexes at these electrode locations. On the other hand, in diaphragmatic peri-infarction block the terminal QRS force is slightly posteriorly directed; R-prime deflections are recorded only low on the right anterior side of the chest and not in the region of the V_1 and V_2 electrodes. Another difference is shown in Figure 1 in which it can be seen that the terminal force in diaphragmatic peri-infarction block is usually more vertically directed than it is in most cases of right bundle branch block.

The tracing shown in Figure 6A illustrates, what at present is believed to be, the characteristic appearance of the QRS complexes in diaphragmatic peri-infarction block when associated with QRS prolongation. It can be seen that the QRS complex in lead I has a terminal S wave similar to that seen in right bundle branch block, however, there is no terminal R-prime at V_1. No preblock or preinfarction tracings were available in this case, however, a large infarction of the diaphragmatic region of the left ventricle was found at autopsy a few days after this tracing was recorded.

It was suggested earlier that perhaps diaphragmatic peri-infarction block might occur without the initial QRS complex deformity of infarction; that is, that the terminal QRS force abnormality of peri-infarction block might be present without the Q_2 and Q_3 and Q_f abnormalities. Two cases have been encountered in which this is believed to have taken place. In one case although the clinical picture of myocardial infarction was present, the patient is still living and the presence of infarction cannot be proved.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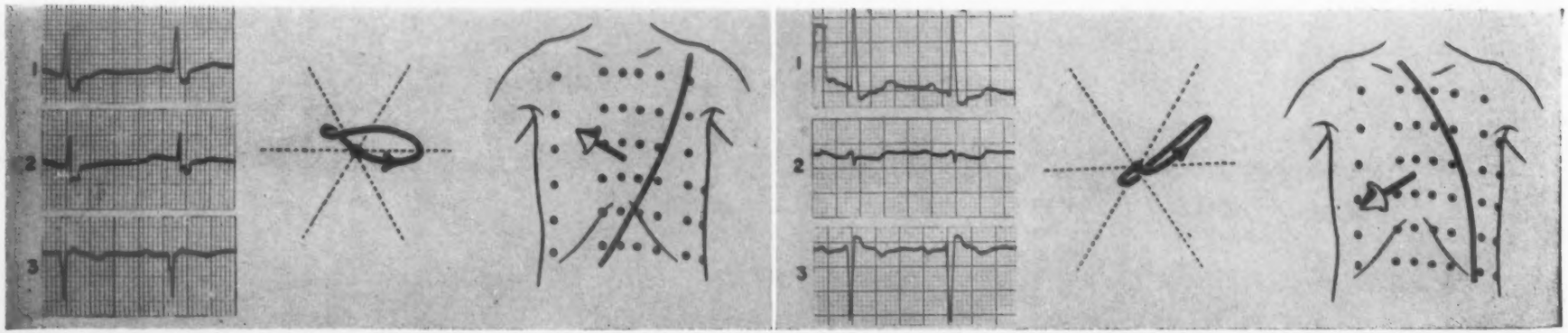
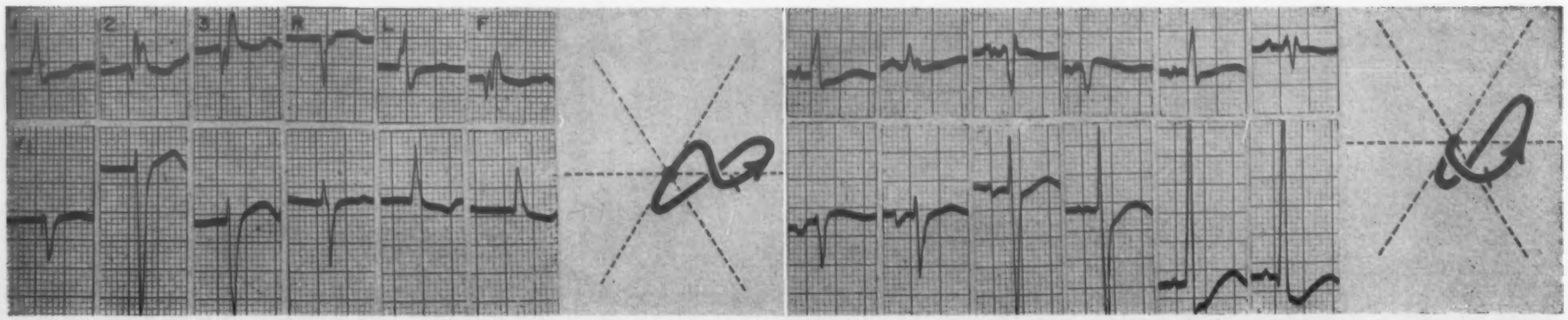


FIG. 5. Direction of the terminal .04 second QRS vector in two cases of right bundle branch block. In these cases the area of relative positivity for this vector occupies a larger region of the anterior chest than it does in the case in Figure 4; it includes the region of the chest where V_1 and V_2 precordial leads are recorded, which means that terminal R-prime reflections would be recorded in these leads.



6A 6B

FIG. 6. Two cases illustrating diaphragmatic peri-infarction block; both cases at autopsy had extensive infarcts of the diaphragmatic surface of the left ventricle. Note how closely the QRS complex in lead I resembles that of right bundle branch block in both cases. In patient H. H. (A) the Q_2, Q_3 and Q_f of diaphragmatic infarction is present; in patient J. B. (B) these initial QRS complex deformities are absent. In both cases the terminal QRS vector is directed slightly rightward and posteriorly with no terminal R-prime at V_1 or V_2.

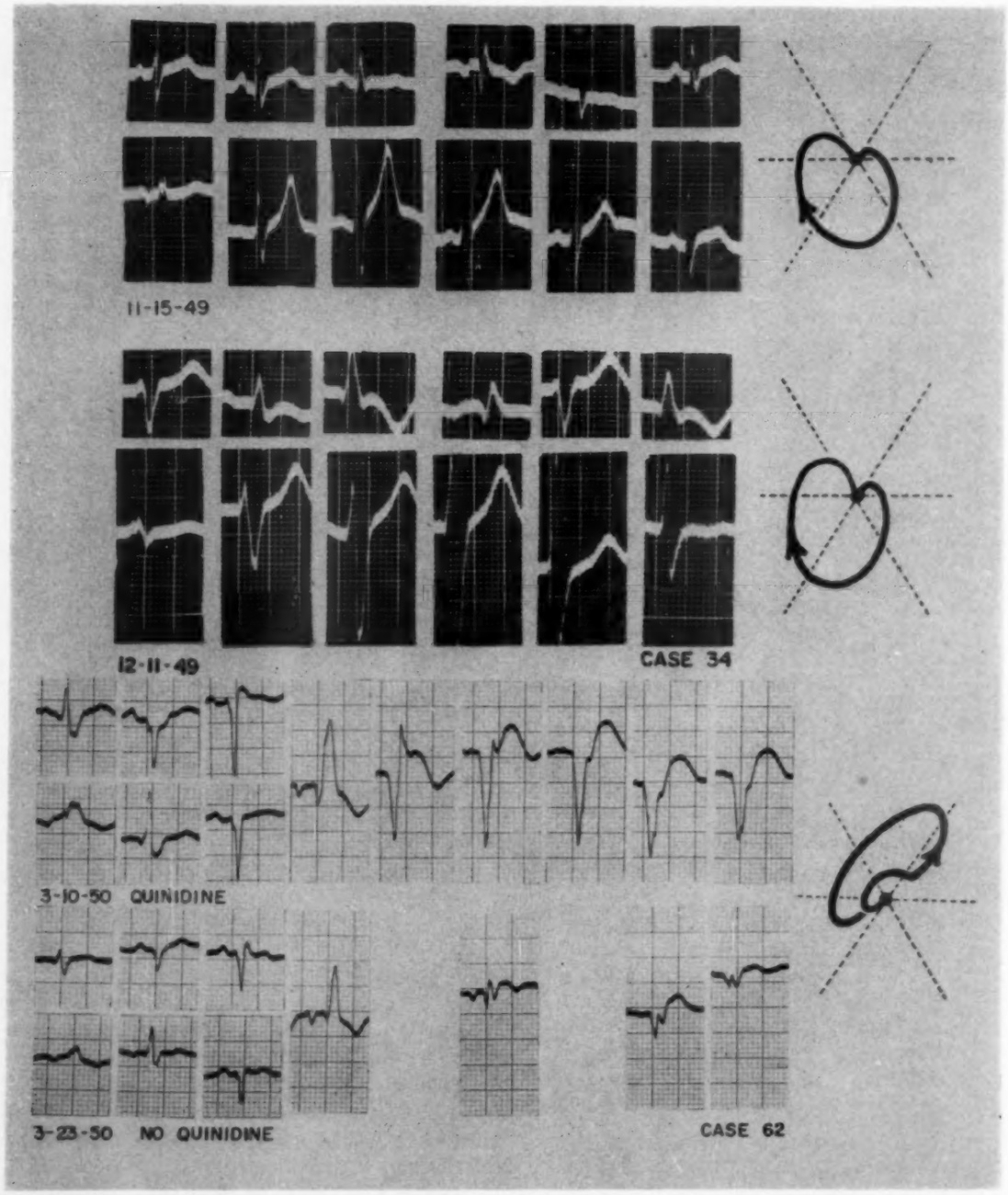


FIG. 7. Two cases demonstrating an unusual type of QRS prolongation due to quinidine. In Case 34 the limb leads are mounted at the top of each tracing in this order: I, II, III, R, L and F. For Case 62 they are mounted to the left of the tracing, the standard limb leads above, the unipolar leads R, L and F below. Precordial leads V_2 and V_4 are missing. Note that during QRS prolongation there is no change in the contour of the QRS loop and that all components of the QRS complexes on each of the leads are equally prolonged.

In the other case, (tracing shown in Figure 6B) the presence of a diaphragmatic infarction with aneurysmal thinning of this region of the left ventricle was demonstrated at autopsy. It can be seen that typical terminal force changes of diaphragmatic peri-infarction block with QRS prolongation are present, but there are no abnormalities of the initial QRS forces, that is, no diagnostic Q waves are present. Preblock or preinfarction tracings were not

available for either of these two cases. Perhaps this is a type of QRS deformity due to infarction which has not been previously recognized. More extensive electrocardiographic–pathologic correlation studies controlled with preblock and preinfarction tracings will be necessary to establish this.

OTHER CAUSES OF QRS PROLONGATION IN MAN

It is generally believed that the QRS prolongation produced by quinidine is simply a type of bundle branch block.[23] Although this may often be true, quinidine may sometimes produce QRS prolongation by mechanisms other than those affecting conduction pathways. (Fig. 7.) The important features of these two cases are that the contours of the QRS complexes remain the same during QRS prolongation and that all parts of the QRS complexes—the initial as well as the terminal—are relatively equally prolonged. In Case 34 the upper tracing shows a normal QRS interval duration with rightward terminal forces in the limb leads. Then, in the lower tracing, with quinidine administration the QRS interval is prolonged to .16 second; the magnitude of certain QRS forces are somewhat increased but the general contour of the QRS loop remains the same. This causes the QRS complex in lead I to have a broad S wave resembling the lead I QRS complex of right bundle branch block. However, while in right bundle branch block only the terminal part of the QRS complex shows prolongation, in this case the initial components of the QRS complex on each of the leads shows as much prolongation as the terminal components. This can best be seen by comparing the Q waves in Leads aVr and III and the R wave in V_2 in the control tracing with those in the tracing taken during quinidine administration. The QRS interval returned to normal duration in this patient when quinidine was discontinued. In Case 62 the upper tracing shows right bundle branch block with anterior infarction and a QRS duration of .20 second during quinidine administration. In the lower tracing quinidine had been discontinued; the right bundle branch block with anterior infarction is still apparent but the QRS interval now measures only .14 second. It can be seen that there has been no change in the contour of the QRS loop and that all parts of the QRS complex are equally shortened following withdrawal of the quinidine.

Since in these two cases the contour of the QRS loop was not altered when QRS prolongation was produced by the quinidine, there can have been no change in the sequence in which the various parts of the heart were depolarized. Therefore, a defect in the conduction pathways cannot have been responsible for the QRS prolongation in these patients. Since all parts of the QRS complex are relatively equally prolonged, depolarization must have been depressed relatively uniformly in all regions of ventricular myocardium by the quinidine. QRS prolongation due to the direct action of agents on heart muscle has been noted in experimental animals before but has not previously been proved to occur in man. This type of QRS prolongation is seen in hypothermia and during hibernation in lower animals.[24,25] It is occasionally the mechanism of QRS prolongation associated with hyperkalemia in man and is the commonest mechanism of the QRS prolongation encountered in the agonal electrocardiogram tracing in man.[26]

COMMENTS

In these three articles a variety of different mechanisms for QRS prolongation have been described. In addition to right and left bundle branch block, peri-infarction block and a diffuse delay occasionally seen with quinidine administraction or with hyperkalemia have been discussed. There are of course many other types of ventricular conduction disturbances in addition to these, but they are not included because of the criteria used for collecting the material for study. For example, the left axis deviation seen in chronic coronary artery disease without electrocardiographic or pathologic evidence of infarction, the marked axis deviations occasionally seen with ventricular hypertrophy, the $S_1S_2S_3$ syndrome of normal young adults and various syndromes associated with a terminal R-prime deflection at V_1 are probably principally due to conduction defects; however, since they are not associated with QRS prolongation they were not collected for control study. That ventricular conduction can be markedly altered without significantly prolonging the QRS interval has been demonstrated in peri-infarction block and undoubtedly there are other major conduction defects in man not associated with QRS prolongation which remain to be clarified.

In addition there are many still unsolved problems in the group of syndromes associated with QRS prolongation. For example, there is

the infrequent case of QRS prolongation with initial QRS forces which are leftward and terminal QRS forces which are superior, slightly rightward and anterior in direction (that is, little or no S_1, large S_2S_3 and terminal R-prime at V_1 and V_2). While some of these cases are manifestly instances of anterolateral peri-infarction block with prolongation, other cases appear to be simple right bundle branch block in the presence of left ventricular hypertrophy. Too few illustrations were encountered in the present series to suggest criteria for differentiating these two diagnostic possibilities. Then, there is the small group of cases of left bundle branch block in which there are marked changes in the direction of the mean QRS axis with the onset of the bundle branch block. This group has been noted by other investigators,[25] and the question arises whether or not these cases are examples of peri-infarction block without the initial QRS force abnormalities of infarction. Unquestionably, careful pathologic study in addition to controlled electrocardiographic sequences will be necessary to solve these and similar problems of importance in clinical electrocardiography.

These studies have leaned heavily on vector methods for interpreting the conventional clinical electrocardiogram. Indeed, the studies would not have been possible without such methods. Vector concepts were introduced into electrocardiography nearly a decade ago, yet a great deal of uncertainty and misunderstanding regarding their role in clinical electrocardiography persists.

The principal source of misunderstanding, and the aspect which has most delayed the use of vector methods in conventional clinical electrocardiography has been the failure to differentiate between the use of vectors as mathematical symbols in electrocardiography and their use for depicting electrical events actually taking place within the heart. There is no question as to the validity of the former use of vector concepts but there is considerable uncertainty regarding the validity of the latter use. Strictly speaking, the vector derived from body surface electrodes defines nothing regarding the electrical activity within the heart. It is simply a graph, a schematization of the distribution of electrical potential on the surface of the body. It is the electrical force which, if generated at the center of the body, would account for the deflections from which it was calculated. Physicists and engineers have used vector methods for describing the distribution of potential within and on the surface of volume conductors for many years. In fact, it is the only method at present available for integrating the electrical measurements obtained from a number of different points on the surface of such a conductor. Thus the use of vector methods simply as a technic for integrating and schematizing the information contained in the various leads of the clinical electrocardiogram is altogether valid and rational.

However, the question immediately arises whether or not this vector may be more than just a graph or mathematical symbol and whether or not it may also be an accurate picture of the magnitudes and direction of resultant electrical activity of a region of the heart. That this might be the case is an intriguing possibility for it would provide an extremely valuable research technic for the study of cardiac electrophysiology. However, this application of vector concepts to electrocardiography is much more uncertain than the application previously described. Before the vector can be considered an accurate picture of intracardiac electrical forces, it must be established that the body surface electrode is accurately recording these events. This has been hotly debated for many years. It involves questions regarding the electrical homogeneity of the body as a conductor, the extent to which the body surface distorts the electrical field surrounding the heart, whether the heart can be treated as a point-source of electrical potential, the effects of the eccentric position of the heart in the chest and many other factors. The important point, however, is that these uncertainties do not bear on the validity of using vector methods to graph the information contained in the various leads of the clinical tracing; these uncertainties are involved only when inferences are made from the graph regarding the electrical activity taking place within the heart.

To understand the use of vector methods for graphing the information in the conventional clinical tracing, it is useful to compare vector methods with other quantitative procedures used in medicine, for example, the glucose tolerance test. In this test a number of samples of blood are obtained at systematically arranged intervals from a randomly selected peripheral vein. Then, with the use of precise chemical methods, the amount of glucose in each sample is measured. The numerical values of these meas-

urements are plotted on a graph giving the "curve" from which the clinical appraisal is made. The curve is comprised of precise numerical values but neither these values nor the curve as a whole refer to the metabolism of any particular tissue or organ. Instead the value of the curve is that it illustrates in quantitative form the results of a procedure which generalizes a highly complex physiologic phenomenon.

Clinical electrocardiography has much in common with this procedure. Here too, a number of "samples" of electrical potential are obtained from systematically selected points on the surface of the body. Since the samples are obtained at some distance from the heart, they are generalizations of the electrical activity taking place within the body. Then, an exceedingly accurate measuring instrument, the galvanometer, is used for measuring the potential manifested in each sample. However, here the resemblance to the glucose tolerance test ends, for, until recently, there was no way in which the quantitative nature of each individual measurement could be used, and there was no way to graph the numerical values from each of the various samples into a single quantitative expression. However, vector analysis now fills this gap, for it provides a mathematical means for utilizing the quantitative values for each sample or lead and for combining these values into a single graph. Instead of a two-dimensional curve, as in the case of the glucose tolerance test, the graph for the clinical tracing takes the form of a system of vectors. In this application no assumptions need be made regarding the electrical activity of the heart or of the electrical characteristics of the body as a volume conductor—any more than in plotting and using a glucose tolerance curve need one make assumptions regarding the glucose metabolism of the liver. In short, the vector concept used in this way is simply a method for giving quantitative form to the results of a procedure which generalizes a highly complex electrophysiologic phenomenon.

This use of vector methods for quantitatively schematizing the information contained in the various leads of the clinical tracing is likely to be the most useful application of vector technics to clinical electrocardiography. It greatly increases the amount of information obtained from a given tracing, and for the first time provides objective and quantitative criteria for comparing and interpreting clinical tracings, as the present studies have illustrated. It is not implied that vector methods should supplant current "pattern" technics for interpreting the clinical tracings, but rather that vector methods should supplement pattern methods. The use of vector technics is helpful in explaining to the beginner why a particular pattern is diagnostic of one or another electrocardiographic syndrome. For the more experienced electrocardiographer they are useful whenever precision of interpretation is necessary for the analysis of the marginally abnormal tracing, for evaluating variations in serial tracings and for the analysis of a complicated or unfamiliar abnormality in the tracing.

SUMMARY

1. Eighty cases of QRS prolongation to .12 second or more due to right ventricular conduction disturbances have been collected. In each case one or more tracings with normal ventricular conduction was also available. This is the first controlled study of the electrical effects of right bundle branch block in man.

2. In all cases the initial electrical forces of the QRS interval were unchanged by the development of right bundle branch block. This is in contrast with the findings in experimental right bundle branch block. Evidence is presented which suggests that the difference is due to the fact that the lesion lies more distally along right ventricular conduction pathways in clinical right bundle branch block than in experimental right bundle branch block. The studies suggest that there is no period when right ventricular excitation is arrested or delayed in clinical right bundle branch block as is commonly believed, but that excitation instantly "leaks" out into the right ventricular myocardium when it reaches the site of the block.

3. These findings confirm the observation made by other investigators that the deformity of the initial QRS forces due to myocardial infarction is not altered by the development of right bundle branch block. Thus "Q wave" criteria for the diagnosis of infarction are valid in the presence of right bundle branch block. The only exception to this is found with strictly posterior infarction, and the reasons for this are discussed.

4. The electrocardiographic syndrome of diaphragmatic peri-infarction block is described and criteria for differentiating it from right bundle branch block, which it closely resembles, are suggested. In addition two cases of diaphragmatic peri-infarction block without de-

formity of initial QRS forces are described. This is a previously unrecognized electrocardiographic manifestation of infarction.

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The Relationship of Displacement of the Esophagus to Left Atrial Volume and Heart Size in Persons with Mitral Stenosis*

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DISPLACEMENT and compression of the esophagus by an enlarged left atrium was first demonstrated by Kovacs and Stoerck[1] in 1910. These investigators made plaster casts of the esophagus at the autopsy table. They also used the roentgenologic technic to observe the outline of the opaque esophagus in the living. They differentiated the esophageal impression of a large left atrium from that of the normal left atrium and also from that of generalized cardiac enlargement. These studies have been abundantly verified. More recently, the roentgenologic anatomy of the esophagus in health and in disease of the heart and great vessels has been comprehensively described by Evans[2] and by Segers and Brombart.[3] Observations of the opaque esophagus have now become a routine part of cardiac study.

Nevertheless, the precise relationship of the degree of displacement of the esophagus to the degree of left atrial enlargement has never been established. The impression has been created that the degree of displacement of the esophagus in mitral stenosis may be used as an index of the degree of left atrial enlargement, provided the displacement is not due to a non-cardiac cause. There is no basis for this opinion because, previous to the introduction of simultaneous biplane stereoscopic angiocardiography, there was no method available to test this assumption in the living.

The purpose of this study is to determine the character of displacement of the esophagus in mitral stenosis with and without cardiomegaly and the relationship of its degree to that of the volume of the left atrium.

MATERIAL AND METHODS

Fourteen women and four men with isolated and significant mitral stenosis, confirmed at the time of mitral valvotomy, were studied. Twelve patients had sinus rhythm, six had atrial fibrillation. Their ages varied from twenty-one to fifty years.

After fluoroscopic examination and orthodiagrams of the heart and opaque esophagus, roentgenograms of the opaque esophagus, using a tube-to-film distance of 6 feet, were obtained in the anterior, right and left anterior oblique and left lateral projections. No significant difference in the outline of the esophagus was noted between the orthodiagrams and the roentgenograms. For this reason the more objective roentgenographic findings are used for this analysis.

Diagrammatic representation of the findings is given in accordance with the method used by Evans.[2]

When displacement of the esophagus is confined to the region of the left atrium, it is regarded as localized. It is regarded as sweeping when the esophagus forms a wide arc, beginning at the inferior margin of the aortic impression and extending to the diaphragm.

The method of Hilbish and Morgan[4] was used to determine the size of the cardiac silhouette in the anterior projection. It is expressed as a percentage of the deviation from normal of the frontal plane area of the heart correlated with the transverse thoracic diameter. A value between minus and plus 25 per cent is considered within the normal range of deviation.

The volume of the left atrium was determined from simultaneous biplane stereoscopic angiocardiograms taken with apparatus devised by Chamberlain.[5] The pictures showing the greatest horizontal and vertical diameters of the left atrium in the anterior projection, and the greatest horizontal diameter of the left atrium in the lateral projection, were used. In order to compare the volume thus obtained with that of the cardiac volume determined by Rohrer's

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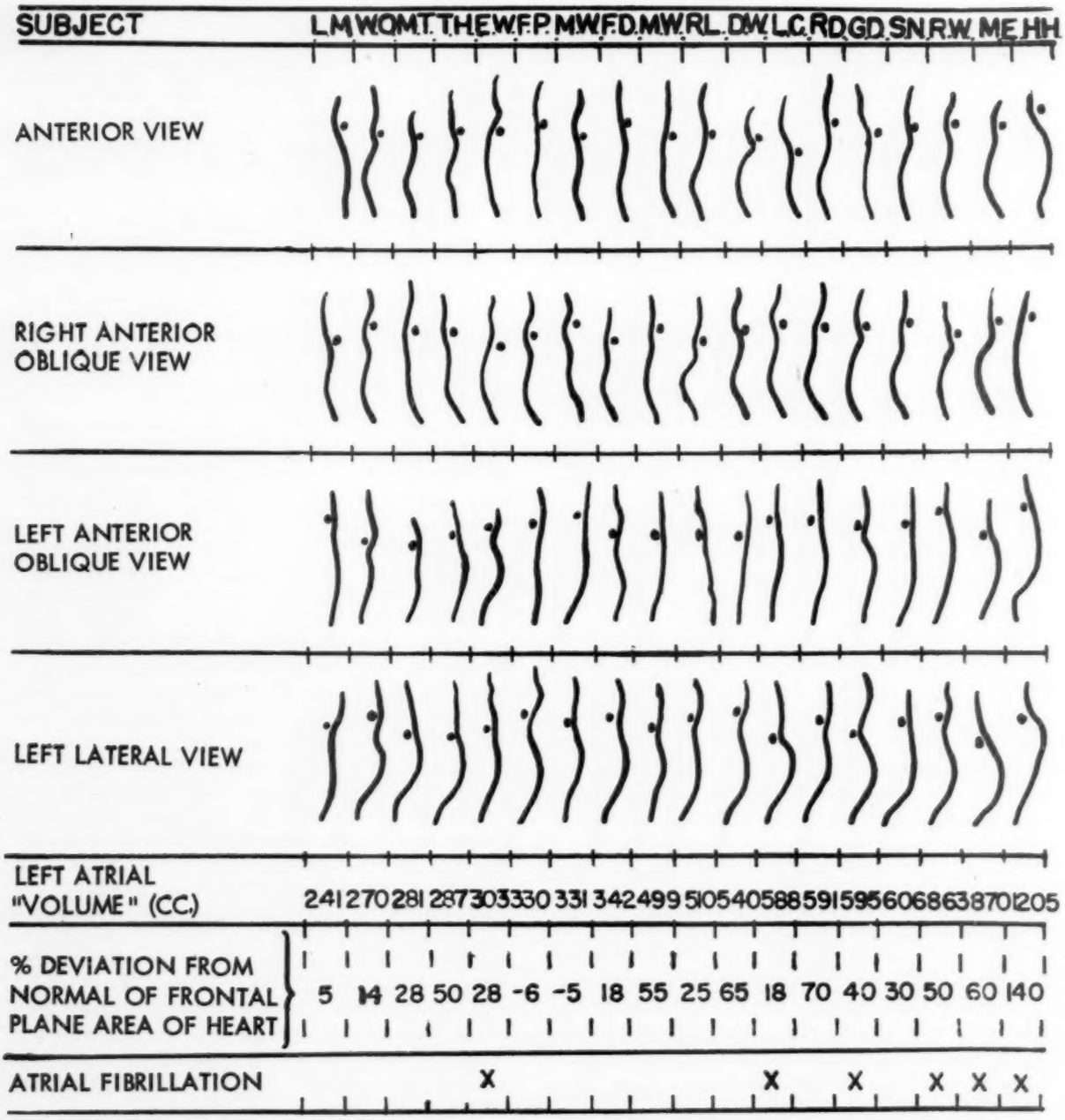

FIG. 1. Line drawings of the barium-filled esophagus of each subject in four projections, arranged according to the volume of the left atrium. The lines are drawn on the left margin of the barium-filled esophagus in the anterior and right anterior oblique projections and on the right margin in the left anterior oblique and lateral projections. The region of the left main bronchus is indicated by a dot. Also shown is the angiocardiographic left atrial volume in cubic centimeters, size of the heart in terms of percentage deviation from normal of the frontal plane area correlated with the transverse thoracic diameter, and the presence of atrial fibrillation.

method, the factor 0.63 should be used.[6] Accordingly, a measured "volume" of 100 cc. in the normal becomes 63 cc. Of course, this does not include the distortion factor of a tube-to-film distance of 100 cm. which would further decrease the volume. This computed volume of the normal left atrium approximates that derived by postmortem study.[5] We, however, do not use a factor to correct the measured volume because of the inability to define the left atrium as a constant geometric structure.

RESULTS

Figure 1 shows the border of the barium-filled esophagus of each subject in four projections, arranged according to the volume of the left atrium. The percentile deviation of the frontal plane area correlated with the transverse thoracic diameter is shown below the left atrial volume. Subjects with atrial fibrillation are indicated by a cross (X).

The left atrium was larger than normal in all eighteen patients. Its volume varied from 241 to 1,205 cc. In seven subjects, however, in whom the left atrial volume varied from 241 to 588 cc., heart size was normal. Only with a left atrial volume larger than 590 cc. was heart size always increased. Even in these instances there was no correlation between the degree of enlargement of the left atrium and that of the heart.

In the anterior projection, fifteen subjects had displacement of the esophagus to the right, localized in eleven patients and sweeping in four. One subject, with a left atrial volume of 1,205 cc., had displacement to the left because the esophagus was adherent to the descending thoracic aorta. The remaining two patients, with left atrial volumes of 241 and 330 cc., had no displacement of the esophagus.

In the right anterior oblique projection, all but one patient had displacement of the esophagus, it was localized in twelve subjects and sweeping in five. In this one patient, with a left atrial volume of 281 cc., the esophagus was not displaced in this projection.

In the left anterior oblique projection, twelve subjects had displacement of the esophagus; it was localized in five persons and sweeping in seven. Displacement of the esophagus was not noted in the other six subjects who had left atrial volumes from 330 to 606 cc.

In the left lateral projection, seventeen patients had displacement of the esophagus, it was localized in fifteen subjects and sweeping in two. In the remaining one, with a left atrial volume of 241 cc. displacement of the esophagus was not evident in this projection.

The incidence of the finding of localized displacement of the esophagus in these persons was greatest in the left lateral projection. However, this projection failed to show such a displacement in one subject who had a left atrial volume of 241 cc. and in whom a localized displacement of the esophagus was noted in the right anterior oblique projection. In two other subjects, with left atrial volumes of 606 and 870 cc. it revealed sweeping displacement of the esophagus rather than localized displacement that was present in at least the right anterior oblique projection.

The left lateral projection was also advantageous in the demonstration of the degree of localized displacement. In only one instance was localized displacement of the esophagus greater in another projection. This was seen in the anterior projection of a person with a left atrial volume of 540 cc.

Figure 1 clearly shows that there is no correlation between the degree of displacement of the esophagus and the volume of the left atrium. Practically identical displacements were frequently seen with left atrial volumes varying as much as fourfold. Correlation between displacement of the esophagus and the volume of the left atrium was absent even in persons with normal heart size.

Enlargement of the heart was associated invariably with sweeping displacement of the esophagus in at least one of the projections other than the left anterior oblique. In this projection, sweeping displacement occasionally occurred without increase in heart size.

COMMENTS

A detailed description of the roentgenologic anatomy of the esophagus in health and in disease is given by Evans.[2] It is sufficient to state here that the normal aortic and left bronchial impressions are often fused into one when mitral stenosis is present. The esophagus usually is slightly to the right, and rarely to the left, of the posterior bulge of the left atrium. It is not firmly attached to pericardium overlying the left atrium. Indeed, the esophagus rarely may change from a right to left displacement spontaneously.[3] It can also be displaced by the aorta and by abnormal mediastinal structures. The character and degree of displacement can also be changed by any method that changes the longitudinal intrathoracic diameter, such as deep expiration or the recumbent position. It is because of the variable position of the esophagus that several projections are necessary before one can be certain that the esophagus is not significantly displaced. Like other investigators,[7,8] we find the left lateral projection best for demonstrating the presence and degree of localized displacement of the esophagus. But the degree of displacement could not be used as an index of the degree of left atrial enlargement.

Most important, the angiocardiographic studies show that the left atrium enlarges maximally from side to side, an enlargement that cannot be recognized by the posteriorly situated esophagus, so that the left atrial volume is always underestimated when displacement of the esophagus is used as standard.

Finally, cardiac enlargement in mitral stenosis tends to convert a localized displacement of the esophagus into a sweeping one.

CONCLUSIONS

1. An enlarged left atrium in individuals with mitral stenosis displaces the esophagus.
2. This displacement of the esophagus is characteristic when confined to the region of the left atrium and is usually best seen in the left lateral projection.
3. As the heart enlarges there is a tendency for this displacement of the esophagus to lose its characteristic localized form that persists longest in the left lateral projection.
4. There is no relationship between the degree of displacement of the esophagus and the volume of the left atrium.
5. There is no definite relationship between the volume of the left atrium in mitral stenosis and the size of the heart.
6. The left atrial volume is almost always larger than that estimated by the degree of displacement of the esophagus.

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Anticoagulant Therapy of Acute Myocardial Infarction*

An Evaluation from Autopsy Data with Special Reference to Myocardial Rupture and Thromboembolic Complications

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THE beneficial effects of anticoagulant therapy in decreasing the thromboembolic complications which commonly follow myocardial infarction have been described in many publications.[1–6] Published data also indicate that the likelihood of myocardial rupture and fatal hemopericardium is increased by the use of anticoagulants,[7–11] although an experimental study of acute myocardial infarction in dogs does not support this conclusion.[12]

Anticoagulant therapy of acute myocardial infarction has been used at Barnes Hospital since 1945. The records of 108 autopsied patients who received this therapy are now available for evaluation of its effects. Data on these patients, added to the published results of others, may help to determine the value and the hazards of anticoagulant therapy.

MATERIALS AND METHODS

The autopsy records of the Department of Pathology of Washington University and the clinical records of Barnes Hospital from 1910 through 1954 were examined. In the period before anticoagulant therapy for acute myocardial infarction had been introduced (1910 to 1945) there were 174 autopsied patients on whom an anatomic diagnosis of acute myocardial infarction had been made (hereafter referred to as Period I patients). In the period after the introduction of anticoagulant therapy there had been 326 autopsied patients with acute myocardial infarction (hereafter referred to as Period II patients). Of these 326 patients, 108 had received anticoagulants and 218 had not.

Data obtained from the autopsy protocol included the age and sex of the patient, the weight of the heart and the incidence of intracardiac mural thrombi, coronary arterial thrombi, extracardiac thrombi or thrombo-emboli, healed myocardial infarcts, myocardial rupture and hemopericardium. From the clinical records data were obtained concerning the duration of anticoagulant therapy and the time at which this therapy was instituted in relation to the time of onset of clinical symptoms of myocardial infarction. Prothrombin activity of the treated patients was available in almost every instance. In each case the survival time after clinical evidence of the onset of infarction was estimated.

RESULTS

Thrombi. Demonstration at autopsy of intracardiac mural thrombus, pulmonary embolus or systemic arterial embolus is considered in this study as evidence of thrombosis complicating acute myocardial infarction. Coronary arterial thrombi and mural aortic thrombi are not considered complications of myocardial infarct. The leg veins were examined in only a few patients and therefore data on thrombi at this site are not included in our report.

Comparative data concerning thrombi occurring in the 500 patients with acute myocardial infarction are presented in Table I. The incidence of thrombi is approximately the same in the patients in Period I (66 per cent) and Period II (59 per cent). Among the patients in Period II treated with an anticoagulant and those not treated the incidence of thrombi was also similar; separation of the treated group into those who received adequate therapy (prothrombin activity 30 per cent of normal or less) and those who received inadequate therapy failed to demonstrate a difference in the incidence of thrombi in the various groups of patients.

However, no thrombi were demonstrated in

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TABLE I

INCIDENCE OF THROMBI AND EMBOLI IN 500 AUTOPSIED PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

	No. of Patients	Mural Thrombi	Pulmonary Emboli	Systemic Emboli	Without Thrombi
Period I (1910–1945)	174	95 (55%)	46 (26%)	43 (24%)	59 (34%)
Period II (1946–1954)	326	136 (42%)	73 (22%)	92 (28%)	135 (41%)
Without anticoagulants	218	88 (40%)	55 (25%)	66 (31%)	91 (41%)
With anticoagulants	108	48 (44%)	18 (17%)	25 (23%)	44 (41%)
Inadequate therapy	31	14 (45%)	4 (13%)	8 (26%)	11 (35%)
Adequate therapy	77	34 (44%)	14 (18%)	17 (22%)	33 (43%)
Therapy begun after three days	23	12 (52%)	8 (35%)	8 (35%)	5 (22%)
Therapy begun within three days	54	22(40%)	6 (11%)	9 (17%)	28 (52%)

TABLE II

INCIDENCE OF THROMBI IN PATIENTS WHO SURVIVED MORE THAN THREE DAYS AFTER CLINICAL ONSET OF MYOCARDIAL INFARCTION

	No. of Patients	With Thrombi	Without Thrombi
Period I (1910–1945)	126	89 (71%)	37 (29%)
Period II (1946–1954)	222	143 (64%)	79 (36%)
Without anticoagulants	133	90 (68%)	43 (32%)
With anticoagulants	89	53 (60%)	36 (40%)
Inadequate therapy	15	12 (80%)	3 (20%)
Adequate therapy	74	41 (55%)	33 (45%)
Therapy begun after three days	23	18 (78%)	5 (22%)
Therapy begun within three days	51	23 (45%)	28 (55%)

TABLE III

AVERAGE SURVIVAL TIME AFTER CLINICAL ONSET OF MYOCARDIAL INFARCTION IN PATIENTS WHO SURVIVED MORE THAN THREE DAYS

	Survival Time of Patients with Thrombi (days)	Survival Time of Patients without Thrombi (days)
Period I patients	14	11
Period II patients without anticoagulant therapy	17	14
Period II patients with anticoagulant therapy begun within three days of onset	12	15

TABLE IV

INCIDENCE OF HEMOPERICARDIUM AND MYOCARDIAL RUPTURE

	No. of Patients	Patients with Hemopericardium and Rupture		
		Total	Without Rupture	With Rupture
Period I (1910–1945)	174	7	0	7
Period II (1946–1954)	326	31	13 (4%)	18 (5.5%)
Without therapy	218	12	7 (3.2%)	5 (2.3%)
With therapy	108	19	6 (5.5%)	13 (12%)
Inadequate therapy	31	5	0	5 (16%)
Adequate therapy	77	14	6 (7.8%)	8* (10%)

* One patient had a septal rupture without hemopericardium.

twenty-eight (52 per cent) of the fifty-four adequately treated patients in whom anticoagulant therapy was started within three days of the clinical onset of myocardial infarction. Absence of thrombi was recorded in only 41 per cent of the 218 untreated Period II patients.

This difference in incidence of thrombi between the latter two groups of patients is more apparent when patients who died within three days after the clinical onset of myocardial infarction are omitted. (Table II.) The absence of thrombi was demonstrated in twenty-eight (55 per cent) of the fifty-one Period II patients who survived more than three days and who were given adequate anticoagulant therapy within the three-day period following clinical onset of infarction. The absence of thrombi were demonstrated in only forty-three (32 per cent) of the 133 untreated Period II patients who survived more than three days.

The group of twenty-three adequately treated Period II patients on whom therapy was begun after three days had a rather high incidence of

TABLE V

COMPARISON OF CLINICAL AND AUTOPSY DATA ON 500 PATIENTS WITH AND WITHOUT MYOCARDIAL RUPTURE

	No. of Patients	Sex	Average Age (yr.)	Average Weight of Heart (Gm.)	Presence of Fresh Thrombi in Coronary Arteries (%)	Absence of Marked Narrowing of Coronary Arteries (%)	Presence of Healed Infarct (%)	Presence of Mural Thrombi (%)	History of Angina (%)	Known History of Hypertension (%)	Hypertension on Admission (%)	Average Survival (days after onset)
Patients without rupture	475	M, 318 (67%) F, 157 (33%)	62	515	38	13	41	46	50	63	50	10.7
Patients with rupture	25	M, 19 (76%) F, 6 (24%)	66	489	72	16	40	36	60	80	68	7.4

thrombi; thrombi were found in eighteen patients (78 per cent).

The average survival (in days) after onset of clinical symptoms of patients who survived more than three days after infarction was determined in the Period I patients, Period II patients without anticoagulant treatment and Period II patients with adequate treatment begun within three days of infarction. No significant differences in days of survival were demonstrated among these three groups. (Table III.)

Myocardial Rupture. The incidence of myocardial rupture among the 500 patients with acute myocardial infarction is 5 per cent. No significant difference between the incidence in Period I and Period II patients could be demonstrated. (Table IV.) The incidence in Period II patients given anticoagulant therapy was thirteen (12 per cent) of 108 patients, a significantly different incidence from that (2.3 per cent) in the untreated Period II patients. Surprisingly, the incidence of myocardial rupture was approximately the same in the adequately and inadequately treated patients.

Other comparative data on the patients with acute myocardial infarction with and without myocardial rupture are given in Table V. In this series the incidence of myocardial rupture was somewhat greater among men than women, as compared to the proportion of men to women in the entire 500 cases of acute myocardial infarction and in the entire series of adult patients subjected to autopsy.[13] The average age of the patient, the average weight of the heart, the incidence of healed infarct and the incidence of marked luminal narrowing of the coronary arteries were all similar both in the patients with myocardial rupture and without. Intracardiac mural thrombi were not significantly less common in patients with rupture. A recent thrombus occluding a coronary artery was found in 72 per cent of the patients with myocardial rupture and only in 38 per cent of those without rupture. It is possible that this difference in incidence of thrombi is not real, as it may be the result of more thorough gross pathologic examination of the heart with a spectacular rupture. A history of hypertension was obtained in 80 per cent of the patients with myocardial rupture and only 63 per cent of the patients without rupture. A recorded blood pressure higher than 150 mm. Hg systolic or 90 diastolic was present on admission or after onset of clinical symptoms of myocardial infarction in 68 per cent and in 50 per cent of the patients in the two groups, respectively. A recorded blood pressure higher than 150 mm. Hg systolic or 90 diastolic was present on admission in 50 per cent of anticoagulant-treated patients and in 48 per cent of untreated patients in Period II.

The average time at which myocardial rupture occurred was on the seventh day after clinical onset of infarction. The site of rupture was the left ventricle in twenty-one patients, the right ventricle in three patients and the interventricular septum in one patient. Left and right ventricular rupture occurred at approximately the same ratio as the occurrence of left and right ventricular infarction in the entire 500 cases (left ventricle 364 patients, right ventricle forty-eight patients).

Hemopericardium without Myocardial Rupture. Sanguinous pericardial fluid was present at autopsy in seven (3.2 per cent) of the 218 untreated Period II patients and in six (7.8 per cent) of the seventy-seven adequately treated Period II patients. This fluid was never described in the autopsy protocol as "blood," but always

as "bloody," "blood tinged," "serosanguinous" or "fibrinosanguinous," and was never estimated as being greater than 300 cc. In our series there are no cases of massive, fatal hemopericardium in anticoagulant-treated or untreated patients without myocardial rupture.

COMMENTS

The entire beneficial effect of anticoagulant therapy cannot be evaluated from autopsy data. Obviously, fatal cases are usually patients who have the most extensive disease process and are more likely to show poor results with any therapy. However, only combined clinical and autopsy data offer a sufficiently exact means of evaluation of clinical results and these are the basis of the present study.

Thrombi. Thrombi complicating acute myocardial infarction were demonstrated at autopsy in a greater percentage of Period II patients who did not receive anticoagulants than in patients who received adequate anticoagulant therapy begun within three days of clinical onset of infarction. (Table I).

The difference in incidence of thrombi in these two groups is 23% (this difference is significant; P less than 0.01) when care is taken to establish comparable groups of patients by omitting those who died within the first three days after clinical onset of infarction. (Table II.) This omission is justified because a much greater proportion of untreated than treated patients died within the first three days after onset of infarction and because thrombi are less common in patients who die early in the illness. The duration of survival affects the incidence of thrombosis.

Seventy-eight per cent of the twenty-three patients in whom anticoagulant therapy was begun more than three days after onset of symptoms had thrombi at autopsy. The high incidence of thrombi in this group may be due to the clinical selection of some patients in whom there was evidence of a thrombiembolic complication.

The incidence of thrombi was not affected if initiation of anticoagulant therapy was delayed more than three days after clinical onset. This finding suggests that anticoagulant therapy is not effective in reducing thromboembolic complications of acute myocardial infarction unless therapy is begun within the first three days after clinical onset.

Our data demonstrate no significant difference (P = 0.3) in the overall incidence of thrombi between Period I and II patients. The beneficial effect of anticoagulant therapy was not great enough to effect a significant overall decrease in incidence of thrombi when used in such a small proportion of patients with acute myocardial infarction.

Myocardial Rupture. The incidence of myocardial rupture complicating acute myocardial infarction in our series is five times greater in anticoagulant-treated than in untreated Period II patients. This difference is highly significant (P less than 0.01) and similar to the results of others.[1,10] However, the possibility that the difference is the result of selection of patients for treatment cannot be entirely eliminated because the difference in incidence of myocardial rupture between Period I patients and all Period II patients (treated and untreated) is not significantly different (P = 0.7). The frequency of myocardial rupture, even in anticoagulant-treated patients, is too small to effect an overall significant increase in incidence between Period I and Period II patients, but might effect an increase if a greater percentage of patients were treated with anticoagulants. Improved medical treatment might possibly explain the infrequency of myocardial rupture in Period II patients not given anticoagulant therapy, although this difference in incidence between Period I patients (4 per cent) and untreated Period II patients (2.3 per cent) is not statistically significant (P = 0.3).

This possibility regarding the selection of patients also exists in the interpretation of the data reported by Waldron et al.[10] Their data show no increase in overall incidence of myocardial rupture between Period I (7.7 per cent) and Period II (7 per cent) patients (treated and untreated).

We were unable to determine a basis for the clinical selection of patients to receive anticoagulants which might influence the occurrence of myocardial rupture. Hypertension was present on admission in similar percentages of treated and untreated patients. Omission of patients who died within the first three days after clinical onset of infarction did not appreciably alter our results. We were also unable to explain why the incidence of rupture in our series was similar in inadequately and adequately treated patients, unless the amount of anticoagulant that can act as a factor in increasing the likelihood of myocardial rupture is less than the amount needed for effective antithrombotic therapy.

Hemopericardium without Rupture. Bloody fluid in the pericardial sac was discovered at autopsy in thirteen Period II patients in whom there was no evidence of myocardial rupture. In no instance did this fluid appear to be present in sufficient amount to have been of primary importance in the cause of death. No significant difference in the incidence of hemopericardium without rupture was found between anticoagulant-treated and untreated Period II patients. Neither hemopericardium nor bloody pericardial fluid was described in the autopsy protocol of any Period I patient not having myocardial rupture. Bloody fluid in the pericardial sac may not have been recorded by the autopsy prosectors in that period.

SUMMARY

The effects of anticoagulant therapy are evaluated from clinical and autopsy data on 500 patients with acute myocardial infarction. Intravascular thrombi were demonstrated at autopsy in a significantly greater percentage of inadequately treated patients than in treated patients. This difference is apparent only when patients who died within three days of clinical onset of infarction are omitted from the comparison. Our data indicate that therapy is not effective unless begun within three days of clinical onset of infarction.

Myocardial rupture occurred five times as frequently among anticoagulant-treated patients as among untreated patients in the same period. However, no significant overall increase in myocardial rupture occurred during the years 1910 to 1954. The possibility exists that selection of patients receiving anticoagulant therapy accounts for the high incidence of rupture but no support for this explanation was found in the clinical histories. The incidence of myocardial rupture in untreated patients decreased slightly in the years 1910 to 1954.

Hemopericardium without myocardial rupture was not significantly more frequent in patients treated with anticoagulants, and in no instance was the amount of blood considered sufficient to have caused death.

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Exacerbation of Lupus Erythematosus Following Splenectomy in "Idiopathic" Thrombocytopenic Purpura and Autoimmune Hemolytic Anemia*

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THE association of autoimmune hemolytic anemia and of thrombocytopenic purpura with disseminated lupus is well known. In fact, it has become increasingly apparent that when either of the first two conditions is present one should think of disseminated lupus as a possible underlying disturbance even in the absence of such objective phenomena as the characteristic rash or the joint manifestations. With the development of the L.E. test a convenient and reliable method for the diagnosis of this "collagen" disorder has become readily available. We have utilized this test as a routine measure in every case presenting autoimmune hemolytic anemia, "idiopathic" thrombocytopenic purpura, idiopathic neutropenia, splenomegaly of undetermined origin, or the like. That the L.E. test occasionally gives negative results in the presence of disseminated lupus has become increasingly evident, especially when the patient is receiving cortisone therapy.

Some cases resist all attempts, clinical and hematologic, at establishing a definitive diagnosis of disseminated lupus. In the three cases presented here, two of autoimmune hemolytic anemia and one of "idiopathic" thrombocytopenic purpura, the diagnosis became apparent only after splenectomy had been performed, following which the various indications of the disseminated disease developed. It is the purpose of this communication to present the clinical and laboratory details of these cases and to discuss some of the possible implications involved.

CASE REPORTS

CASE 1. Mary K. (N.E.C.H. No. 64-934). This twenty year old white single girl was first seen in October, 1951, in consultation at the Lynn Hospital because of menorrhagia and thrombocytopenia. In September, 1950, x-ray therapy to the face was administered because of severeacne. In June, 1951, the patient complained of some stiffness and limited motion of the finger joints, especially marked in the morning. In September, bleeding from the gums occurred and the patient noted numerous ecchymoses of the legs and arms following slightest trauma. In October, the menstrual period was very profuse and bleeding continued for about two weeks. At this time there was a short bout of fever, the temperature rising on one occasion to 103°F. Studies of the blood demonstrated marked thrombocytopenia.

Upon examination, the patient looked well and had good color. A few petechiae of the gums and mucous membranes were present. Neither the liver nor the spleen was felt. There was no peripheral lymphadenopathy. A few of the finger joints showed questionable spindling. Numerous small ecchymoses of the thighs and upper extremities were present, together with a few petechiae of the lower extremities and below the clavicles. The skin of the face showed the pitted scars of severe acne in the past. No other eruption was noted.

Blood studies revealed a definite reduction in platelets. No abnormal white cells were seen. The red cells were essentially normal. Aspirated sternal marrow showed normal cellularity with granulocytic hyperplasia. Megakaryocytes were numerous and platelet production was diminished. The diagnosis of "acute" idiopathic thrombocytopenic purpura was made, although the possibility of a more fundamental

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disease such as disseminated lupus was considered. An L.E. preparation was negative.

Therapy with ACTH was then instituted, at first in a dosage of 25 mg. four times daily. This was continued for three weeks, following which cortisone was given for maintenance. There was a striking improvement during the next two months and the platelets rose to levels of about 100,000 per cu. mm. However, with small doses of cortisone (12.5 mg. twice daily) there was recurrence of bleeding from mucous membranes and the patient was admitted to the New England Center Hospital on December 19, 1951.

On admission the patient looked well but showed numerous petechiae of the mucous membranes and small ecchymoses of the extremities. Laboratory studies revealed: red blood cell count 3.54 million, hemoglobin 10.1 gm., reticulocytes 2.6 per cent, white blood count 12,400 with a normal differential formula. The platelets numbered 25,000 per cu. mm. The prothrombin concentration was 60 per cent of normal. The Coombs' and L.E. tests were negative. The tourniquet test and bleeding times were prolonged. Heterophil agglutination test was positive in a dilution of 1:112.

Therapy with 20 mg. ACTH every eight hours was begun and by December 24, 1951, the platelets had increased to 250,000 per cm. The red blood cell count increased to 3.65 million and the hemoglobin to 11.7 gm. Bleeding decreased promptly and again the patient was discharged on maintenance steroid therapy, at first in a dosage of 100 mg. cortisone daily.

When cortisone was discontinued in February, 1952, relapse occurred again with return of bleeding from the gums and into the skin. Arthralgia of the hands and wrists was also noted. The patient was readmitted to the hospital for the second time on February 29, 1952. The physical and hematologic findings were approximately the same as those noted previously, with a platelet level of 37,000 per cm. L.E. preparations were again negative. No albumin was noted in the urine; the sediment was negative. The sedimentation rate was 116 mm./hour. Administration of cortisone was resumed in a dosage of 200 mg. daily and on the fourth hospital day, following two transfusions of plastic bag blood, splenectomy was performed. The spleen weighed 185 gm. and appeared normal on gross examination. Unusually prominent follicles and a decrease in the intervening red pulp were visible in the cut sections. The typical vascular and perivascular "onion skin" lesions of disseminated lupus were present.

Within twenty-four hours after operation the platelets increased to over 1 million per cu. mm. On the sixth postoperative day there was an episode of dyspnea, fever and left pleural effusion believed to be consistent with pulmonary infarction. Conservative anticoagulant therapy was given and the patient responded satisfactorily.

After discharge from the hospital, the patient was maintained on 25 mg. cortisone per day. She felt well for about four months but in July, 1952, interscapular and upper sternal pleuritic pain and fever occurred. On examination the patient appeared acutely ill. Her temperature was 101°F., pulse rate 105 per minute.

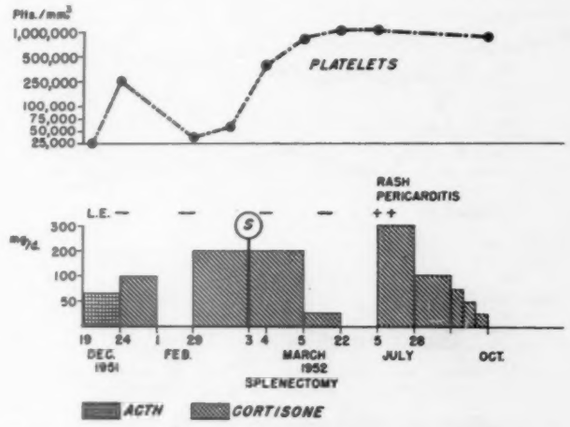

FIG. 1. Case 1. "Idiopathic thrombocytopenic purpura"; splenectomy followed by complete remission in thrombocytopenia, but typical features of disseminated lupus erythematosus developed.

A faint diffuse macular rash was evident over the abdomen and lower chest. Several 1 by 1 cm. nodes were present in the left axilla. A pericardial friction rub was heard. Decreased breath sounds were noted at the right base and fine rales were present at the left base. There was no purpura. The laboratory studies showed red blood cell count 4.06 million, hemoglobin 12.5 gm., reticulocytes 0.5 per cent, white blood cell count 8,900 with a normal differential formula. Platelets varied between 1 million on admission and 2.1 million on discharge. The sedimentation rate was 110 mm. in the first hour. Small numbers of red cells and leukocytes were present in the urinary sediment. Electrocardiogram and x-ray changes, consistent with pericarditis with effusion, were seen.

Therapy on this admission again included bed rest and administration of cortisone, 300 mg. per day. The patient's temperature ranged initially as high as 101°F. but all blood cultures were negative. After one week of cortisone therapy the patient's temperature returned to normal, the pericardial friction rub disappeared and the patient showed rapid improvement. Cortisone dosage was decreased to 100 mg. per day without recurrence of the disease. One of two L.E. preparations was positive. The patient was discharged on July 28, 1952, on a regimen of cortisone, 100 mg. per day. When last seen on October 7, 1952, the patient continued in good health with a platelet level of 800,000 per cu. mm. and a sedimentation rate of 34 mm. per hour. At that time the patient was taking 25 and 50 mg. cortisone on alternative days. This was

eventually discontinued and the patient has remained well to the present writing.

CASE II. Priscilla E. (N.E.C.H. No. 58-517.*) This patient, a thirty-five year old white woman, was first admitted to the New England Center Hospital on April 17, 1951, for severe anemia. In October, 1950,

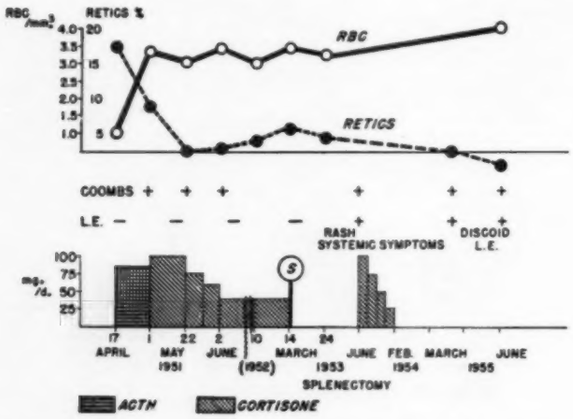

FIG. 2. Case II. "Idiopathic acquired autoimmune hemolytic anemia"; splenectomy followed by complete remission in hemolytic anemia, but typical features of disseminated lupus erythematosus developed.

the patient noted increasing fatigue and pallor. At about the same time she complained of pain in the fingers, shoulders and back of the neck, together with slight swelling of the finger joints. For about two weeks prior to admission she had noted jaundice, anorexia and low grade fever. She had fainted once or twice. Just prior to admission to the hospital, liver extract and iron had been given and several blood transfusions had been administered.

On admission to the hospital the patient appeared acutely ill with a temperature of 105°F., pulse 120, respirations 24, blood pressure 114/72. There was icterus of the skin and sclerae, but no petechiae or ecchymoses. Three small flame-shaped hemorrhages were noted in the right fundus, one with an area of central pallor. A few shotty nodes were palpated in the cervical, axillary and inguinal areas. The liver and spleen were palpated just below the costal margins.

The hemogram on admission revealed a red blood cell count of 1.0 million, hemoglobin 3.4 gm., and reticulocyte count of 17 per cent. The white blood cell count was 13,000 with a shift to the left. Occasional stippling and Howell-Jolly bodies were noted. Five nucleated red cells per 100 white cells were seen. Erythrocyte fragility study showed a marked shift to the left (beginning at 0.6 per cent sodium chloride) with several red-cell thickness populations. The blood sedimentation rate was 147 mm./hour. The fecal urobilinogen was 533 mg. per day. A very pronounced erythroid hyperplasia was observed in the bone marrow. The urinalysis was normal with a specific gravity of 1.015. Several L.E. preparations were negative. The serum bilirubin was 1.8 mg. per cent (1.4 mg. per cent indirect) initially. The serum total protein, albumin and globulin were normal. The cephalin flocculation test was 4 plus, and the thymol turbidity 4.8 units. The direct Coombs' test gave a positive reaction; and free auto- and iso-agglutinins were detected at 37°, 20° and 3°. Both the heterophil agglutination test and the serologic test for syphilis gave positive results, the former in a 1:112 dilution. The chest x-ray was negative.

Therapy was begun on admission with 2 units of washed packed red cells and ACTH, 80 units per day, intramuscularly. Response was immediate. By discharge on May 1, 1951, the red blood cell count was 3.3 million, hemoglobin 11.7 gm., and reticulocytes 8 per cent. The patient had had a good clinical and hematologic remission and was discharged on a regimen of cortisone, 100 mg. per day, which was gradually reduced to 50 mg. daily.

On May 22, 1951, the patient was readmitted to the hospital with a three-day history of pain and tenderness in the left groin, nausea, vomiting and fever. There was marked tenderness in the left popliteal fossa and left groin indicating probable thrombophlebitis. Therapy with rest, anticoagulants and penicillin was instituted, following which there was prompt clearing and the patient was discharged June 2, 1951, on a regimen of 50 mg. cortisone per day. During the latter part of 1951 and throughout 1952 the patient was in remission on small doses of cortisone, although the Coombs' test remained positive in a dilution of 1:4. Occasional swelling and tenderness in the left knee was noted. The L.E. preparations remained negative.

During early 1953, the patient complained of excessive roundness of the face produced by the cortisone therapy and requested splenectomy. This was performed on March 14, 1953. The spleen weighed 180 gm. Microscopically there was a wide range in the size of the lymph follicles and the early "inflammatory" changes of disseminated lupus were noted; so slight, however, as to have been missed at the first examination. The hemoglobin rose from a preoperative level of 10.2 gm. with a reticulocyte count of 8 per cent to a hemoglobin of 12 gm. and a reticulocyte count of 1.5 per cent on March 21, 1953. The blood counts have remained stable to date.

In June, 1953, the patient noted a mild rash over the nose which spread rapidly when a sun lamp was used for home treatment. Increasing fatigue, slight fever, anorexia and weight loss occurred and there was a recurrence of multiple joint pains with some limited motion of the finger joints. Examination on June 16, 1953, showed the typical butterfly eruption of lupus erythematosus and spindling of the

* This case has already been reported.[1]

finger joints. The L.E. preparations, previously negative, were now positive. Cortisone was again administered beginning with 100 mg. per day and continued in decreasing amounts as the rash warranted until it was finally discontinued in February, 1954. During the rest of 1954, the hemograms and urinalyses were normal and cortisone was discontinued. However, in early 1955 the rash had spread to the forehead and down the face, and the typical features of "discoid" lupus were now evident. Hemoglobin was 11 gm., the reticulocytes 2.5 per cent, the platelets 1 million, the white blood cell count 8,700 with 7 per cent band forms, 58 per cent mature granulocytes, 26 per cent lymphocytes and 16 per cent monocytes.

When the rash extended onto the back and arms chloroquine diphosphate was given to the patient and there was considerable improvement in the rash. In March, 1955, the red blood cell count was 3.07 million, hemoglobin 11.9 gm., reticulocytes 1.2 per cent, platelets 690,000 per cu. mm. and white blood cell count 7,900 with a normal differential formula. The L.E. preparation was positive. No further cortisone was given.

CASE III. Albertina G. (N.E.C.H. No. 73-241.) This fifty-three year old woman was first admitted to the New England Center Hospital on November 11, 1952, complaining of easy fatigue for about five months prior to admission. Later she noted palpitation and dizziness and on one occasion had fainted. For about one year the patient had noted that exposure to sunlight seemed to precipitate arthralgia of the hands, feet and ankles.

The past history included many operations, among others appendectomy and uterine myomectomy in 1936. Subsequently pelvic tuberculosis had been discovered. In 1938 several lymph nodes, presumed to be tuberculous, were removed from the left cervical area. In 1941 right salpingectomy for "adhesions" was performed and in 1942, a hysterectomy and left salpingectomy were done. Following this an inguinal abscess developed with continued drainage and the patient was hospitalized in a sanatorium for three and one-half years with the diagnosis of tuberculosis. During this time the right hip was fused because of tuberculous involvement.

Upon admission to the New England Center Hospital there was notable pallor and slight icterus of the skin and sclerae. The liver edge was felt 2 cm. and the spleen 1 cm. below their respective costal margins. Numerous scars of previous operations were noted.

Laboratory data on admission revealed a red blood cell count of 1.45 million, hemoglobin 4.8 gm. and hematocrit 18 per cent. The reticulocytes were 25 per cent, the platelets 162,000 and the white blood cell count 7,250 with a normal differential formula. The sedimentation rate was 152 mm. in the first hour. Erythroblastic hyperplasia was evident in the bone marrow. Peripheral blood smears showed three nucleated red cells per 100 white cells and there was much stippling. The total serum bilirubin was 1.8 mg. per cent with 1.5 mg. per cent of the indirect variety. The stools were guaiac-negative. The chest x-ray was normal. X-rays of the right hip revealed bony

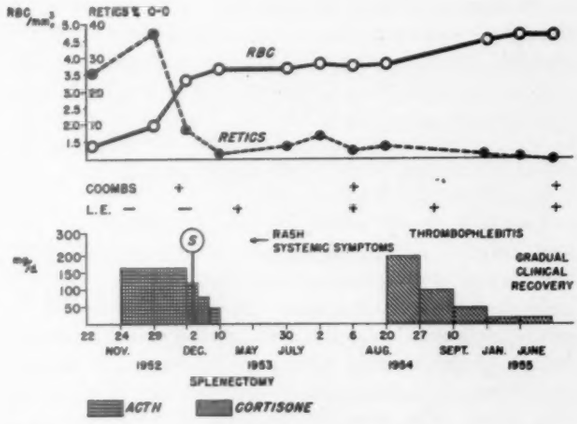

FIG. 3. Case III. "Idiopathic acquired autoimmune hemolytic anemia"; splenectomy followed by complete remission in hemolytic anemia, but typical features of disseminated lupus erythematosus developed.

fusion. The cephalin flocculation test was 4 plus and the thymol turbidity 1.5 units. The total serum protein was 7.2 gm. per cent with normal albumin and globulin. The urine was normal except for a trace of albumin.

The Coombs' test gave a positive reaction by both tube and slide method; there was a 2 plus agglutination with titration of the antiglobulin serum in a 1:64 dilution. Studies of the patient's serum for free antibodies demonstrated a warm agglutinin at 37°C. in a 1:256 dilution, a 2 plus agglutination in bovine albumin at 22°C. in a 1:16 dilution, and a 3 plus (auto) agglutination in trypsin-treated cells at 3°C. in a 1:4 dilution. L.E. preparations were negative.

On November 24, 1952, administration of ACTH was begun in a dosage of 160 units per day. This was continued in gradually decreasing dosage through December 9. The red blood cell count increased from 1.45 million to 3.3 million, the hemoglobin from 4.8 gm. to 11.2 gm. and the reticulocytes decreased from 25 per cent to 7 per cent. The platelets rose from 162,000 to 374,000. Since long-term steroid therapy appeared potentially dangerous on account of the history of tuberculosis, splenectomy was decided upon and performed on December 2, 1952. The spleen, which weighed 190 gm., showed vascular changes consistent with lupus erythematosus and marked hemosiderosis. In the eight days subsequent to operation the red blood cell count rose to 3.6 million, the hemoglobin to 12.2 gm., and the platelets to 600,000. The reticulocytes dropped to 1 per cent. On discharge

on December 10, 1952, the sedimentation rate was 5 mm. in the first hour and the serum bilirubin 0.4 mg. per cent.

The patient was clinically well and maintained stable blood counts through May, 1953. At about that time she noted a rash on the areas of skin exposed to the sun, together with some pains and slight swelling in the fingers. The patient had no further symptoms though the mild arthralgia continued over the summer and fall. During September, 1953, she began to note slight fatigue but since the blood counts were stable no therapy was prescribed. During September, stiffness of the fingers increased and peculiar sensations were noted in the legs. At this time a positive L.E. reaction was obtained for the first time.

During February, 1954, there was marked anorexia and weight loss. A rash had developed over the abdomen and arms and there was slight fever. In March, pain developed in the right side of the chest and low grade fever continued. Cervical, axillary and inguinal lymph nodes became enlarged. In July, the hemoglobin began to drop and an increase in reticulocytes was noted. On readmission to the New England Center Hospital the patient was extremely ill, emaciated and almost unrecognizable. An acute thrombophlebitis of the right lower leg was present. The chest x-rays revealed minimal pleural effusion at both bases. The thrombophlebitis responded satisfactorily to conservative measures. Because of the recurrence of mild hemolytic anemia as indicated by a drop in hemoglobin and red cell count together with slight reticulocytosis, administration of cortisone was again begun on August 20, 1954, but was "covered" with para-aminosalicylic acid and streptomycin in the attempt to avoid recurrence of tuberculosis. The L.E. preparation was positive, the urine showed a trace of albumin with 1 or 2 red blood cells and white blood cells. The blood urea nitrogen was 11 mg. per cent. The erythrocyte sedimentation rate was 71 mm. in the first hour and the Coombs' titration was 2 plus in a dilution of 1:2.

With continued therapy there was gradual improvement in all symptoms, a slow gain in weight and subsidence of arthralgia. The blood counts are now normal.

COMMENTS

That disseminated lupus may masquerade under the guise of such apparently unrelated conditions as arthritis, disease of the kidneys, purpura and non-bacterial endocarditis has been clear for a number of years. Some patients with all the features of "idiopathic" thrombocytopenic purpura without any vestige of disseminated lupus, have shown the typical features of that disorder in the sections of spleen removed at operation. Similarly, some patients who at first had the characteristic features of apparently typical rheumatoid arthritis or subacute nephritis, or who had splenomegaly, leukopenia or simply a positive reaction to the serologic test for syphilis, were eventually found to have disseminated lupus. Such situations recur most frequently with the so-called collagen disorders and to a lesser extent in certain cases of leukemia, notably in chronic lymphocytic leukemia, lymphosarcoma and Hodgkin's disease.[2] One should therefore consider the collagen disturbances, leukemia and "lymphoma," in many hematologic disorders, especially when splenomegaly, leukopenia or thrombocytopenia are present, and perform the L.E. test routinely under these circumstances. Occasionally, the observer is rewarded by a positive L.E. test. Such was not the case in the patients discussed in this paper.

In the three cases herein described, two of autoimmune hemolytic anemia and one of "idiopathic" thrombocytopenic purpura, the possibility of an underlying disseminated lupus was seriously considered in all prior to splenectomy. In Case I, the patient with "idiopathic" thrombocytopenic purpura, arthralgia of the finger joints was noted. In Case II, a patient with hemolytic anemia, there was a history of arthralgia and laboratory evidence of multiple sensitizations was present. In Case III, there was an old history of tuberculosis. However, none of the patients had any definitive indications of disseminated lupus and repeated L.E. tests were consistently negative. Nevertheless, following splenectomy in all three the various clinical manifestations of disseminated lupus became clearly evident and reactions to the L.E. tests were positive.

In Case I, in which characteristic histologic lesions of lupus were present in the cut sections of spleen, the symptoms of high fever, weakness, acute pericarditis with effusion and pleural effusion developed about four months after splenectomy. These symptoms subsided rather promptly when cortisone was administered in the usual dosage of 300 mg. daily. In Case II, in which autoimmune hemolytic anemia and various other indications of multiple sensitization were present (positive heterophil agglutination test, positive serologic tests for syphilis, and so on), the typical butterfly eruption of lupus and arthralgia with limited motion of the fingers and wrists developed three months after splenectomy. In Case III, a patient with autoimmune hemolytic anemia, a slight skin eruption and arthralgia

developed about six months after splenectomy. The patient later showed marked weight loss, fever, pleurisy with effusion, generalized lymphadenopathy, a generalized skin eruption and renal changes. The L.E. test first became positive in these three cases when the lesions of disseminated lupus became manifest—after splenectomy.

Since no definitive evidence of this disease could be detected with the spleen intact, and since exacerbation of the lupus took place with the spleen removed, one must consider that splenectomy had removed a staying or inhibitory effect of that organ on the disease. Such an effect of the spleen is not completely unknown in other diseases. Thus in apparently healthy rats splenectomy is usually followed by the development of a severe, generally fatal hemolytic anemia due to bartonellosis.[3] This infectious process, latent in most rat colonies, can only be bred out from certain strains by careful selection. A number of experimental studies, especially by the technic of parabiosis, have indicated that the controlling effect of the spleen in bartonella infection is mediated through a humoral factor.[4] With the spleen intact, the bartonella infection is latent, becoming widely disseminated only after splenectomy. Similar observations have been recorded in studies of malaria in man, splenectomy being followed by activation of a previously latent process.

We have postulated that the spleen is an inhibitory organ to the bone marrow, normally in a regulatory fashion, but when enlarged resulting in cytopenias: neutropenia, thrombocytopenia and anemia.[6] In the normal subject splenectomy is followed by slight though definite increases in red cell, leukocyte and platelet values. However, when the spleen is removed in the presence of continued hemolysis or hemorrhage, striking changes take place in the blood picture including the appearance of nucleated red cells, myelocytes, bits of megakaryocytes and the like. These effects of splenectomy in the presence of certain abnormal conditions are perhaps comparable to the development of the wide dissemination of lupus seen in the cases mentioned herein after the same operation. They indicate the possibility that the spleen produces or contains certain humoral factors that are important in regulating marrow growth, and perhaps in preventing the dissemination of certain infectious or non-infectious conditions. Lauda[7] discusses this possibility at length in his book on the normal and pathologic physiology of the spleen.

In the cases reported in this paper one of the steroids had been given for some period prior to splenectomy and had been discontinued two to four weeks after splenectomy. The appearance of a positive L.E. test following discontinuance of cortisone has been reported after the sudden withdrawal of this medication in certain cases of arthritis.[8] Whether these cases described by Slocumb represented lupus fundamentally or whether withdrawal of the medication resulted simply in the appearance of the L.E. factor is obscure. The disseminated lesions of lupus were not present and the positive L.E. test was demonstrated very shortly after cortisone withdrawal. This is quite different from the cases in the present series in which evidences of severe lupus appeared only after a few to several months, when the L.E. test was simultaneously positive for the first time. It must be conceded that while exacerbation of the lupus took place after splenectomy, this is no proof that it was due to that event. Nevertheless, the development of severe and typical disseminated lupus following splenectomy in patients who previously had only the latent disease is a striking situation which merits some attention and further study.

SUMMARY

A report is made of three patients showing either autoimmune hemolytic anemia or "idiopathic" thrombocytopenic purpura in whom, after previous therapy with cortisone, splenectomy was followed by overt manifestations of disseminated lupus erythematosus. Prior to splenectomy L.E. tests were negative and only a few suggestive symptoms of lupus were present. After splenectomy, L.E. tests were positive and the widely disseminated lupus became apparent.

The possibility is discussed that the intact spleen in these cases had a controlling effect on the disease, and that splenectomy led to exacerbation of the lupus by removing a possible controlling mechanism.

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Observations on Hepatic and Renal Dysfunction in Trichinosis*

Anatomic Changes in These Organs Occurring in Cases of Trichinosis

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TRICHINOSIS is a disease caused by the dissemination of trichinella larvae throughout the body. The larvae are known to travel in lymphatics and then to enter the blood stream. This knowledge helps to clarify the varied and frequently puzzling clinical picture presented by this disease. Hall[1] points out the potential difficulties in diagnosis and lists about fifty diseases or conditions which have been diagnosed in patients who eventually were shown to have trichinosis.

Early in the history of this disease emphasis was placed on the findings of muscular involvement, ocular and respiratory abnormalities and eosinophilia. However, case reports in recent years have indicated that involvement of the nervous system and viscera is responsible for the more serious consequences of the infection; nevertheless, the systemic nature of the disease in its severe form is not fully appreciated.

It is the purpose of this paper to add to the clinical and pathologic studies on trichinosis by reporting a series of cases in which functional and pathologic derangements in the liver and kidney will be stressed. It is not our purpose to belabor well established observations.

CASE REPORTS

CASE 1. E. J., a forty-five year old barber, was admitted to the White River Junction Veterans Administration Hospital on September 19, 1953 because he had a "high fever." The patient had been well until approximately three weeks prior to admission when he had a gastrointestinal upset characterized by nausea, vomiting and diarrhea. The vomiting promptly subsided but the diarrhea persisted with four or five loose, watery, non-bloody bowel movements a day. Approximately ten days prior to admission the patient began to have vague muscle aches and recurrent headaches. He felt dull and tired easily. One week prior to admission he noted swelling of the eyelids, bloodshot eyes and tenderness of the eyeballs when touched or pressed. These symptoms lasted three days. During the third week of his illness the patient began to feel feverish; he had progressive anorexia, felt weak and tired easily. Because of these symptoms he sought medical help. The patient said he had ingested uncooked, pickled pork sausage, which was made locally, about one week before he had observed any symptoms. He also said he usually had a hearty appetite and that he drank about one quart of beer daily. Occasionally he would "go on a binge," but he always ate well when he drank. There was no history of liver or biliary tract disease.

Physical examination on admission disclosed temperature 105°F., pulse 120, respirations 20, blood pressure 150/100. The patient was obese, lethargic, dehydrated and severely ill. Except for slight weakness of the lateral recti of the eye there was a paucity of positive physical findings. The liver edge was nontender and was palpated 1 cm. below the right costal margin. The spleen was not felt. There was no jaundice. There was no muscle tenderness to palpation and the neurologic examination was within normal limits.

The white blood count was 16,150, neutrophils 33 per cent, lymphocytes 5 per cent, eosinophils 62 per cent. The urine was normal. A blood culture was reported as showing no growth. Stool examinations were negative for ova, parasites and enteric pathogens. Serial liver function tests and serum proteins are tabulated in Table 1. A laked venous blood preparation done on the second hospital day revealed the presence of trichinella larvae. (Fig. 1.) Biopsy of the gastrocnemius muscle disclosed encapsulating Trichinella spiralis.

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TABLE I

CASE I

Date 1953	Hospital Stay (no. of days)	Serum Total Protein (gm./100 cc.)	Serum Albumin (gm./100 cc.)	Serum Globulin (gm./100 cc.)	Bromsulfalein Retention after 45 Min. (%)	Cephalin Flocculation Test (24 hr. and 48 hr.)	Thymol Turbidity Test (units)
9/23	5	4.6	2.7	1.9	..	Negative	...
9/28	8	6.0	3.4	2.7	..	.....	...
10/5	15	6.4	3.6	2.8	..	.....	...
			FOLLOW-UP PERIOD				
12/9/53	2 mos.	6.3	3.7	2.6	23	Negative	9.0
3/19/54	5½ mos.	6.9	4.4	2.6	20	Negative	4.7
2/18/55	1½ yrs.	8.3	4.7	3.6	23	.....	7.3

The prominent features during the first few days of hospitalization were high fever, headache and mental lethargy. The treatment was primarily supportive. Aspirin was administered to help relieve the patient's fever and myalgia. It gave such striking relief that on the third hospital day he was started on a course of aspirin, 0.9 gm. every 4 hours. This dose was continued for five days and then reduced to 0.6 gm. every 8 hours for a period of four days. (Fig. 2.) The patient was afebrile by the ninth hospital day. There was marked improvement in mental responsiveness, a return of appetite and freedom from muscle pain, but generalized weakness persisted. The patient was discharged on the eighteenth hospital day.

One month following discharge the patient still complained of easy fatigability and an occasional watery bowel movement. Physical examination at that time revealed a large non-tender liver easily palpated 3 cm. below the right costal margin. This represented a definite increase in the size of the liver since discharge. On subsequent follow-up examinations, two months, six months and one year later, the patient offered no complaints. He was working steadily and felt strong. The physical examination one year following discharge showed the patient to be obese; the liver could not be palpated and there were no obvious stigmata of liver disease. However, liver function tests at that time showed persistent delay in bromsulfalein excretion, with 23 per cent retention of the dye at the end of forty-five minutes.

CASE II. H. S., a forty-four year old butcher, was admitted to the Mary Hitchcock Memorial Hospital on April 11, 1955 with the complaint of "swelling of both eyes." The patient had been in good health until four days prior to admission when he noted swelling of the right upper eyelid. The next morning both eyes were swollen. The swelling was associated with a severe, constant headache behind the eyeballs. The patient also noted that he saw double when he tried to read. Two days prior to admission his temperature rose to 102°F. The patient said he felt "all tired out" and had lost his appetite. The past history and review of systems were non-contributory. The patient said that in recent weeks he had slaughtered locally bred pigs and had used the pork to make sausage. While preparing the sausage he had sampled the uncooked meat from time to time to make sure that it was well seasoned.

Physical examination on admission showed temperature 100.4°F., pulse 82, respirations 20, blood pressure 158/80, weight 214 pounds. The patient was a heavy, muscular white man sweating profusely. There was pronounced edema of both eyelids, marked bilateral conjunctival injection, chemosis and slight proptosis, but no increase in intraocular tension. The optic discs and media were within normal limits. The remainder of the physical examination was not contributory.

On admission the white blood count was 12,100; differential: polymorphonuclear leukocytes 67 per cent, stab forms 6 per cent, lymphocytes 16 per cent, eosinophils 10 per cent and monocytes 1 per cent. Serial chamber eosinophil counts were: April 11, 793/mm.^{3}, April 14, 1,700/mm.^{3}, April 16, 2,900/mm.^{3} No trichinae were seen in three examinations of laked venous blood. Urine analysis on April 11 was normal; urine analysis on April 18 showed the presence of 0.007 gm. albumin/100 cc., 3 to 4 red cells per high power field, 30 hyaline casts per high power field and 20 to 30 coarsely granular casts per high power field. Electrocardiograms taken April 12 and April 18 were interpreted as being within normal limits. Serum protein and liver function studies are listed in Table II.

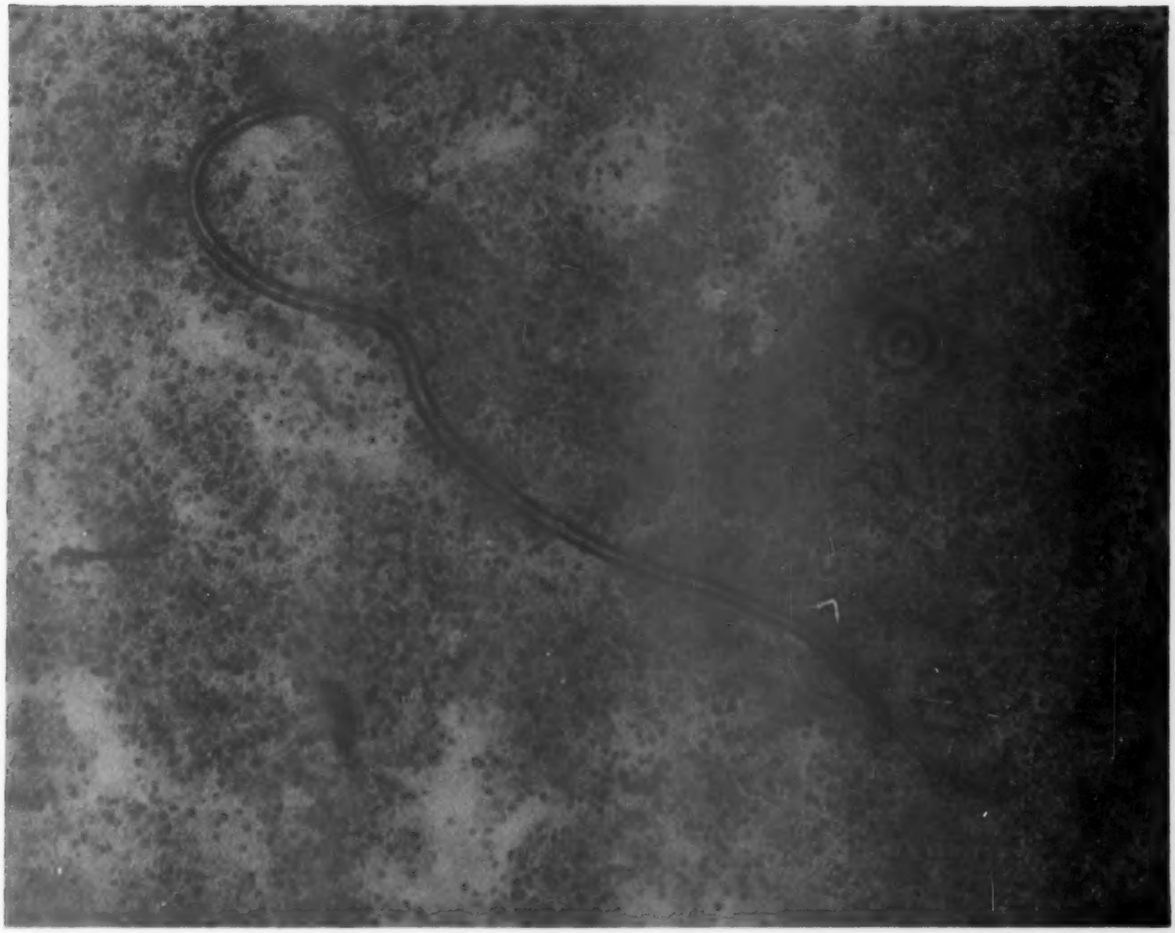

FIG. 1. A trichinella larva recovered from venous blood (original magnification × 50).

The patient received supportive therapy primarily except for aspirin 0.9 gm. every four hours. The periorbital edema and chemosis showed definite improvement within twenty-four hours after instituting aspirin therapy and had subsided significantly by the third hospital day. The fever continued for a period of nine days. On the third hospital day the patient began to have generalized muscle aches and tenderness, most severe in the calves and dorsal cervical muscle groups. The muscle pains were worse when sitting or lying down and the patient said he felt better when moving. He frequently spoke of his tiredness and during the first hospital days had no appetite, partly because all food tasted flat to him. However, in spite of anorexia and a blunted sense of taste he was able, after the second hospital day, to eat a regular hospital diet which was estimated at 2,000 calories per day. A trichinella extract skin test was done on the flexor aspect of the arm on the fifth hospital day. At fifteen minutes there was a 1 cm. wheal with a flare; at twenty-four hours there was a 2 cm. infiltrated plaque. The patient was discharged on the thirteenth hospital day for further convalescence at home.

CASE III. G. G., a forty-year old grain mill laborer, was first admitted to the White River Junction Veterans Administration Hospital on December 31, 1953 with the chief complaint of weakness. The patient stated that he had been in good health until approximately five weeks prior to admission when he first observed easy fatigability, stuffiness in the head and fever. He was seen on December 1 by his family physician who told him he had a "strep throat," although the patient said his throat was not particularly sore. He was given an injection of penicillin and a prescription for oral penicillin which was to be taken for four days. During the next week he continued to have fever and an inflammation developed in the right eye which was diagnosed as acute conjunctivitis. The conjunctivitis was treated with sulfadiazine ointment and it subsided. The oral penicillin was continued for an additional five days. Three weeks prior to admission the patient returned to his usual work of hauling bags of grain. Shortly thereafter pain and tenderness developed in the patient's right calf and there was progressive swelling of the right leg. He returned to his physician on December 21 and a

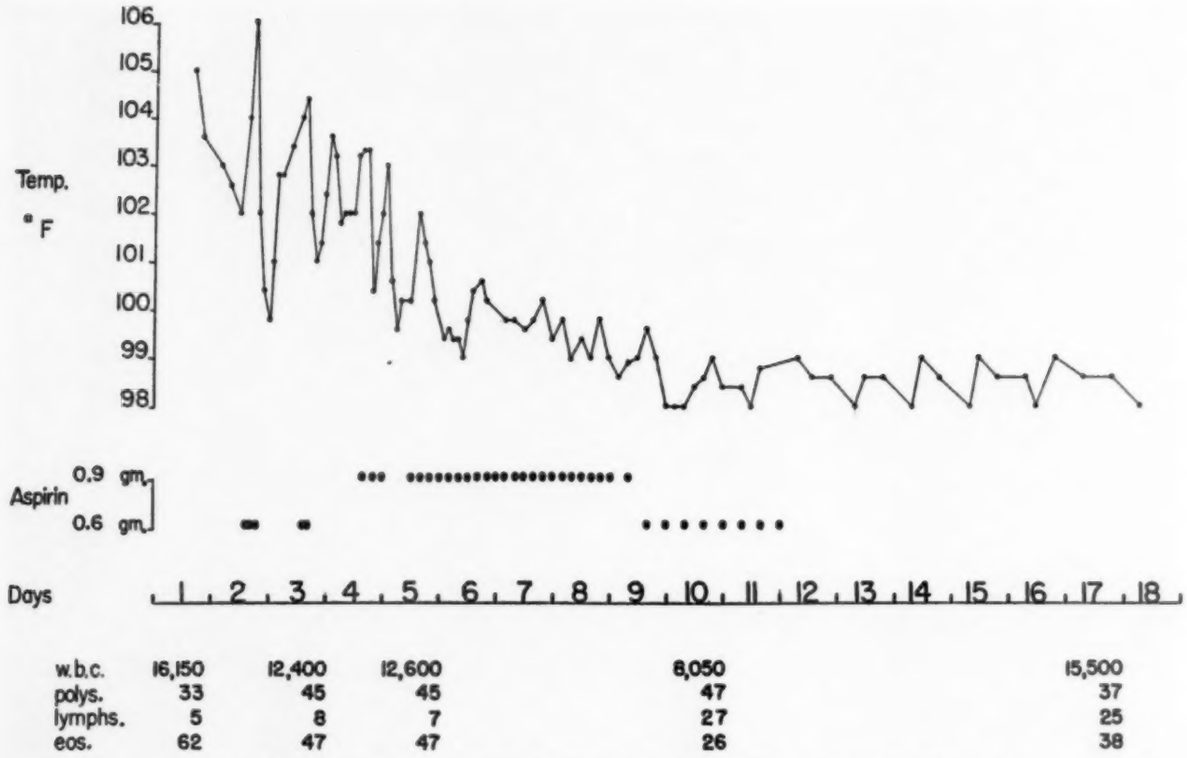

FIG. 2. Temperature and therapy chart for Case 1, patient E. J., September 1953.

TABLE II

Date 1955	Serum Total Protein (gm./ 100 cc.)	Serum Albumin (gm./ 100 cc.)	Serum Globulin (gm./ 100 cc.)	Bromsulfalein (% retention in blood after 45 min.)	Thymol Turbidity (units)
4/13	6.0	4.2	1.8	...	...
4/20	5.1	3.4	1.7	...	0.0
4/22	...	...	...	9.0	...

bilateral thrombophlebitis was diagnosed. At this visit it was also noted that the pharynx was still inflamed and a triple sulfa preparation, bed rest, hot packs and elevation of the legs were ordered. The fever recurred in the week prior to admission, and he became so weak that the least exertion exhausted him. The patient also complained of generalized aches and pains, especially severe in the lumbar area of his back.

On December 28, his physician recorded: "Temperature 99.6°F., blood pressure 140/90, pulse rate 84, severe lethargy, puffiness of the face and a roughened first sound at the apex." Urinalysis was reported to show "numerous cellular casts" and a "2+ albumin." Hospitalization was advised. On admission the patient gave the additional history that for the past week he had not urinated as often as was usual for him. There were no other complaints referable to the urinary system. There was no previous history of kidney disease. During the week prior to admission the patient had progressive loss of appetite and frequent nausea but no vomiting, diarrhea or other gastrointestinal tract disorder.

Review of the patient's past history revealed that at the age of eight he had been told he had "rheumatic fever." During that illness the patient was in bed for a period of three months and all he could remember was that he was "sensitive" all over his body. He could not recall any specific swelling of the joints, chorea or fever. At that time the patient was told he had a heart murmur. However, subsequent school examinations and physical examination at the time of his induction into the army revealed no significant cardiac abnormalities. There were no known allergies.

Physical examination on admission disclosed temperature 98.6°F., pulse 80, respirations 18, blood pressure 150/90. The patient appeared chronically ill. The skin had a pale, waxen color. There were multiple petechial hemorrhages throughout the buccal membranes and hard palate. The pharynx was minimally reddened. The heart was not enlarged, the rhythm was regular and no murmurs were heard

Palpation of the abdomen revealed voluntary spasm and tenderness to deep palpation in the right upper quadrant. No liver edge or mass could be felt. There was striking bilateral costovertebral tenderness to percussion. The peripheral pulses were easily palpated. There was bilateral tenderness in the calves as well as bilateral tibial edema of slight degree. A thrombosed vein was palpated on the dorsal surface of the right foot. The Homans' sign was negative. The remainder of the physical examination was within normal limits.

The white blood count was 11,200; differential: polymorphonuclear leukocytes 65 per cent, lymphocytes 25 per cent, monocytes 9 per cent and eosinophils 1 per cent. The hemoglobin was 12.2 gm./100 ml., and the red blood count 4.1 million/mm.^{3} Urinalysis revealed specific gravity 1.012, pH 4.5, 2+ albumin and a fresh spun sediment showed 5 to 15 white cells per high power field, 10 to 20 red cells per high power field, many granular casts and an occasional red blood cell cast. The initial blood chemistry values were: nonprotein nitrogen 95 mg. per cent, Na^+ 130 mEq./L., K^+ 4.6 mEq./L., Cl^- 100.5 mEq./L. and CO_2 combining power 19.6 mEq./L. Phenolsulfonphthalein excretion was 45 per cent in two hours. In view of his long hospital course subsequent blood and urine studies are shown in Table III. Several blood cultures using various culture media and technics were all negative. Throat culture taken on admission and subsequent throat cultures were not remarkable except for one obtained on the fourteenth hospital day which showed a predominance of beta hemolytic streptococci and Streptococcus viridans. An antistreptolysin titer drawn on the fourth hospital day was more than 2,500 antistreptolysin units. Urine cultures were negative. The chest X-ray, cardiac fluoroscopy and flat plate of abdomen taken on admission were within normal limits. An intravenous pyelogram on the twenty-eighth hospital day showed no function after five minutes and minimal visualization of the dye, bilaterally at thirty minutes. The electrocardiogram taken on admission was within normal limits; however, progressive T wave abnormalities were shown on serial electrocardiograms which were consistent with a diagnosis of a diffuse myocarditis. (Fig. 3.) An intradermal trichinella skin extract test using 0.1 cc. of the antigen performed on the seventy-second hospital day was negative.

The patient's course was characterized by protracted fever, nephritis with uremia, anemia, recurrent thrombophlebitis, evidence of extensive myocarditis, abnormal liver function and mental changes which suggested involvement of the central nervous system. The patient was febrile for a period of sixty-five days.

Initially the nephritis was characterized by oliguria, albuminuria, hematuria, uremia and abnormal serum electrolytes, in particular, hyponitremia. Anemia developed early and several transfusions were re-

TABLE III
CASE III

Hospital Stay (no. of days)	Hemoglobin (gm./100 cc.)	White Blood Count (mm.^{3})	Polymorphonuclears (%)	Lymphocytes (%)	Eosinophils (%)	E.S.R. (mm./hr.)	Serum										Bromsulfalein Retention after 45 Min. (%)	Thymol Turbidity Test (units)	Cephalin Flocculation Test
							Nonprotein Nitrogen (mg. %)	Na^+ (mEq./L.)	K^+ (mEq./L.)	Cl^- (mEq./L.)	CO_2 Combining Power (mEq./L.)	Total Protein (gm./100 cc.)	Albumin (gm./100 cc.)	Globulin (gm./100 cc.)	*Total Cholesterol (mg. %)	Free Cholesterol (mg. %)			
1	12.2	11,200	65	9	1	...	95	130	4.6	101	19.6	...	...	...	.....	....	...	....	.....
5	12.0	12,350	80	17	1	117	128	130	6.0	103	18.6	6.6	...	...	107.0	30.8	...	....	.....
12	10.5	14,350	70	27	3	...	82	143	6.9	...	23.7	4.9	1.8	3.1	.....	....	...	....	.....
21	9.5	10,400	73	18	5	115	71	141	4.6	111	21.9	5.1	1.7	3.4	.....	....	...	10.1	1 + (48 hr.)
40	11.0	13,700	73	24	3	...	43	...	...	...	....	5.0	2.3	2.6	.....	....	...	....	.....
47	9.1	13,500	..	..	..	123	38	136	4.3	105	27.0	5.6	1.8	3.8	.....	....	...	....	.....
64	8.8	13,500	69	24	6	138	..	...	...	...	....	6.7	2.5	4.2	.....	....	9.5	....	.....
86	11.6	9,650	64	31	4	91	41	...	...	...	....	6.7	3.3	3.4	.....	....	6.8	6.6	Negative
One Year Follow-Up	16.5	8,300	53	34	3	13	43	...	...	...	....	7.0	...	...	.....	....	...	6.3	Negative

* Normal Values: Total Cholesterol: 150 to 250 mg./100 cc.
Cholesterol Esters : 25 to 28 per cent free

quired. A biopsy specimen of the left gastrocnemius muscle taken on the twenty-seventh hospital day was reported as normal skeletal muscle.

During the fifth hospital week a harsh, apical systolic murmur suddenly developed in the patient. At this point, in spite of negative blood cultures, it was

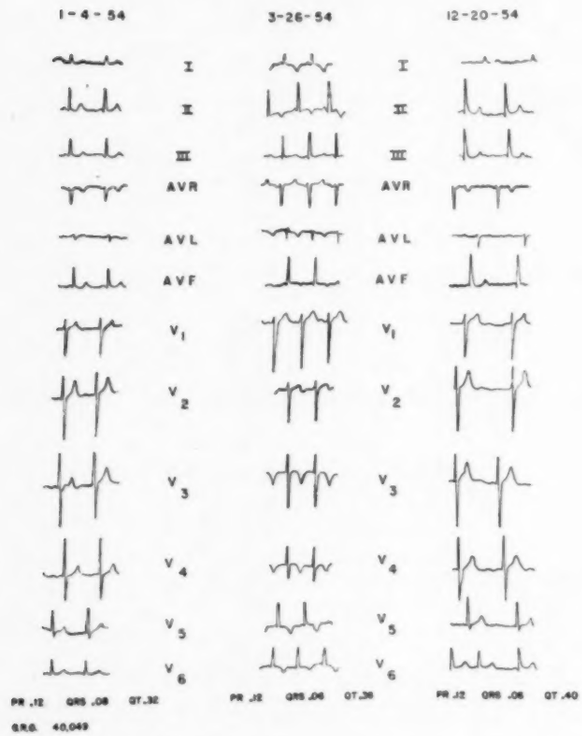

FIG. 3. Case III. Electrocardiographic changes which occurred in a one-year period. The tracing on March 26, 1954 reveals the T-wave abnormalities which developed and was interpreted as being consistent with a diffuse myocarditis. A tracing taken approximately one year after the onset of illness shows a return toward normal.

believed that fever, anemia, nephritis and sudden development of a heart murmur, along with a questionable past history of rheumatic fever, suggested that the patient had subacute bacterial endocarditis. He was given a two-week course of antibiotics, aqueous penicillin, 200,000 units every two hours and streptomycin, 1.0 gm. intramuscularly, twice a day. The treatment was unsuccessful and signs of systemic disease persisted unmodified. Tenderness in the patient's right upper quadrant continued for many weeks, although the liver was never palpable. Liver function studies and serial serum protein determinations are listed in Table III. Involvement of the multiple system suggested a diffuse vascular disease. Extensive diagnostic studies were negative until the sixty-fifth hospital day when a second biopsy specimen of the muscle was taken. The pathology report was as follows: "Microscopic examination reveals normal epidermis and dermis. The subcutaneous tissue contains medium-sized blood vessels, two of which contain organized thrombus. The adjacent muscular tissue shows fibrosis and necrosis of muscle fibers and one section contains a coiled encapsulated Trichinella spiralis. Involved blood vessels are surrounded by lymphocytes. Some of the smaller arterioles also have lymphocytes about them. There are brown pigment-filled macrophages in and adjacent to the necrotic and fibrosed skeletal muscle." (Figs. 4 and 5.)

A recheck of the history revealed that the family had a roast of pork about one week prior to the onset of the patient's illness. He had eaten his portion from the "pink center" of the roast and the outer, more thoroughly cooked portions were given to other members of the family. A young daughter had "bronchitis" a few days after eating the roast and subsequently has shown a positive reaction to the trichinella agglutination test.

The patient slowly improved and was discharged on the one hundred and second hospital day. After discharge the patient continued to improve and gain strength; however he had persistent 1 to 2+ albuminuria. Approximately one year following discharge he was readmitted for evaluation of albuminuria. On this admission the patient was asymptomatic and the physical examination was within normal limits. The hemogram and electrocardiogram were normal. Twenty-four hour urinary albumin excretion was 1.45 gm. An intravenous pyelogram was interpreted as within normal limits. Studies of renal function showed a normal urea clearance (86% of average normal) decreased renal plasma flow (C_{PAH} = 404 ml./min./1.73 M^2) and glomerular filtration rate (C_{Inulin} = 102 ml./min./1.73 M^2).

Cases IV and V were members of a family of five all of whom had severe trichinosis. A brief account of this family epidemic is as follows: The family consisted of the mother, F. LeC., the father, L. LeC., two daughters, A. LeC. (Case IV) and P. LeC. (Case V), and a son, R. LeC. On the evening of October 18, 1944, F. LeC. stuffed a chicken for the Sunday dinner. One ingredient of the stuffing was raw pork. The chicken was not refrigerated and the next morning was roasted for the noon meal. On the night of October 19 chilliness, malaise, vomiting, watery diarrhea, fever and prostration developed in the entire family. Medical attention was not sought for three days. Ten days after the onset of symptoms the entire family was admitted to another hospital with a diagnosis of acute enterocolitis.

F. LeC., the mother, was acutely ill. She had vomited daily, had persistent diarrhea and was unable to retain any nourishment except small teaspoonfuls of liquid. The patient was delirious, had labored respirations, vomited coffee-ground material, went into coma and died within a few hours after admission to the hospital. A medico-legal investigation was begun

FIG. 4. Case III. A coiled, encapsulated trichinella larva seen in a section from deltoid muscle biopsy (original magnification × 261).

FIG. 5. Case IV. A ruptured capillary seen in section from deltoid muscle biopsy (original magnification × 261). It is suggested that such vascular changes play a significant role in producing the clinical and pathophysiologic manifestations of the disease.

and a postmortem examination was ordered. The autopsy, however, was not performed until twenty-four hours after death. Search for heavy metals and other poison was negative. There was severe postmortem tissue autolysis which made interpretation of the histologic sections difficult and questionable and the findings therefore will not be presented. Trichinosis was not suspected and no muscle sections were examined. There was no evidence of enteritis.

The course of the disease in the younger daughter, A. LeC., age eighteen, was similar but more protracted and is presented as Case IV. The patient died December 12, 1944 and a diagnosis of trichinosis was made at autopsy. On December 14, 1944, the remaining members of the family were admitted to the Mary Hitchcock Memorial Hospital.

The father and son survived. No space will be devoted to the detail of their cases except to note that both showed albuminuria and hematuria for a number of weeks. Studies of liver and kidney function were not done. Follow-up studies were incomplete and the patients did not respond to efforts to contact them.

CASE IV. A. LeC., age eighteen, was admitted to another hospital on October 29, 1944, with the history already outlined. Her chief complaints were nausea, vomiting, diarrhea and fever.

Physical examination on admission was not remarkable except that the abdomen was full and rounded, with generalized tenderness over the entire abdominal area. Laboratory data on October 30, 1944: White blood count 8,250; differential: polymorphonuclear leukocytes 76 per cent, stab forms 9 per cent, lymphocytes 12 per cent and monocytes 3 per cent. The hemoglobin was 15.5 gm./100 ml. and the red blood count 4.62 million per mm.^{3} Serial urinalysis showed 0.01 to 0.02 gm. albumin/100 cc., with varying numbers of white blood cells and red blood cells. A urinalysis done December 12, 1944 revealed 0.1 gm. albumin/100 cc. and sediment examination revealed 200 white blood cells and 200 red blood cells per high power field. On November 12, 1944 the serum nonprotein nitrogen was 63 mg. per cent and fasting blood sugar 103 mg. per cent.

Little detail is available on the hospital course of this patient except for the persistence of her initial complaints. She died on December 12, 1944 at 7:45 P.M. An autopsy was performed on December 13, 1944 at 1:00 P.M.

Summary of autopsy findings. A small portion of the diaphragm was digested and several hundred live trichinae larvae were recovered. Grossly the liver, which weighed 1,700 gm., had a mottled red and brown color. The capsule was smooth and glistening. Cut section showed the lobular markings to be distinct.

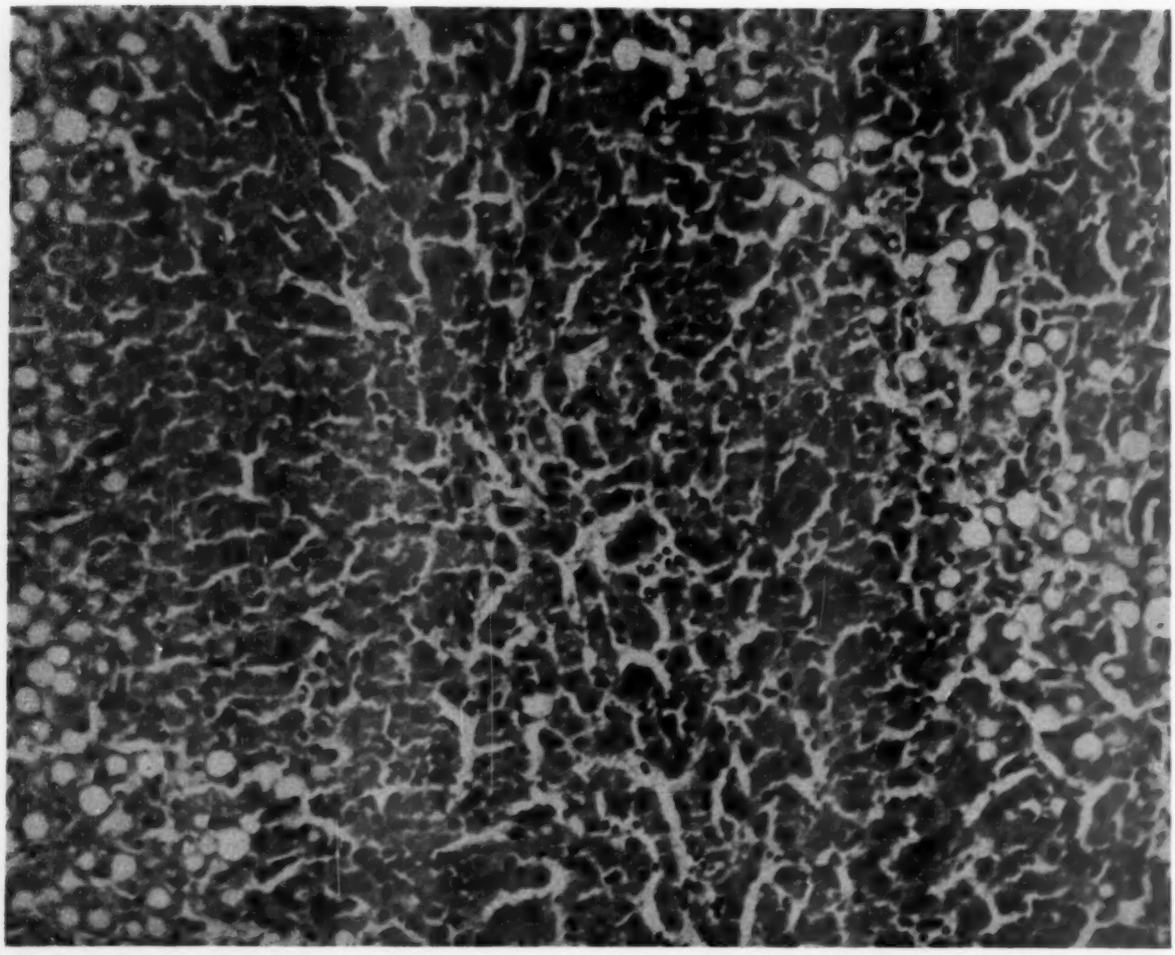

FIG. 6. Case IV. Fatty change in the liver cells at the periphery of the lobule. Hematoxylin and eosin; original magnification, × 790.

Scattered throughout were indistinct mottled, yellow areas. Histologically (Fig. 6) the microscopic examination revealed a moderate to severe degree of fatty change in the parenchymatous cells. The damaged cells were predominantly in the periportal or peripheral portion of the hepatic lobule. Polymorphonuclear leukocytes, eosinophils, lymphocytes and plasma cells infiltrated some of the periportal areas. There was slight increase in the periportal connective tissue. No bile duct proliferation or liver cell regeneration was observed.

The right kidney weighed 220 gm., the left, 230 gm. The capsules stripped with ease. The entire parenchyma was swollen and edematous, bulging over the cut surface of the capsule. The sectioned surface had a mottled yellow, pink and gray color. There was poor differentiation of the cortex and medulla. Microscopic examination (Figs. 7 and 8) showed edema of the interstitial connective tissue of the cortex and medulla. In many sections the epithelial cells lining Bowman's capsule were swollen and a pink granular material was present in the capsular space. Vacuolization was present in the epithelial cells of the proximal and distal tubules. The lumen of many of the tubules contained a granular eosinophilic material. There was a moderate degree of postmortem autolysis.

Other findings at necropsy included myocarditis, encephalitis and bronchopneumonia.

CASE V. P. LeC., age twenty-three, was admitted to the Mary Hitchcock Memorial Hospital on December 14, 1944, because of a "black-out spell." The patient had been in good health until October 19, 1944, when, along with the other members of her family, she experienced acute onset of fever, nausea, vomiting and diarrhea, as already described. The patient remained at her local hospital from October 29 until December 11. She was treated with penicillin, sulfasuxadine, saline and glucose infusions and clysis. Despite this therapy her fever persisted, varying from 99°F. to 102°F. daily. The patient had recurring diarrhea, which was described as "greenish" and "offen-

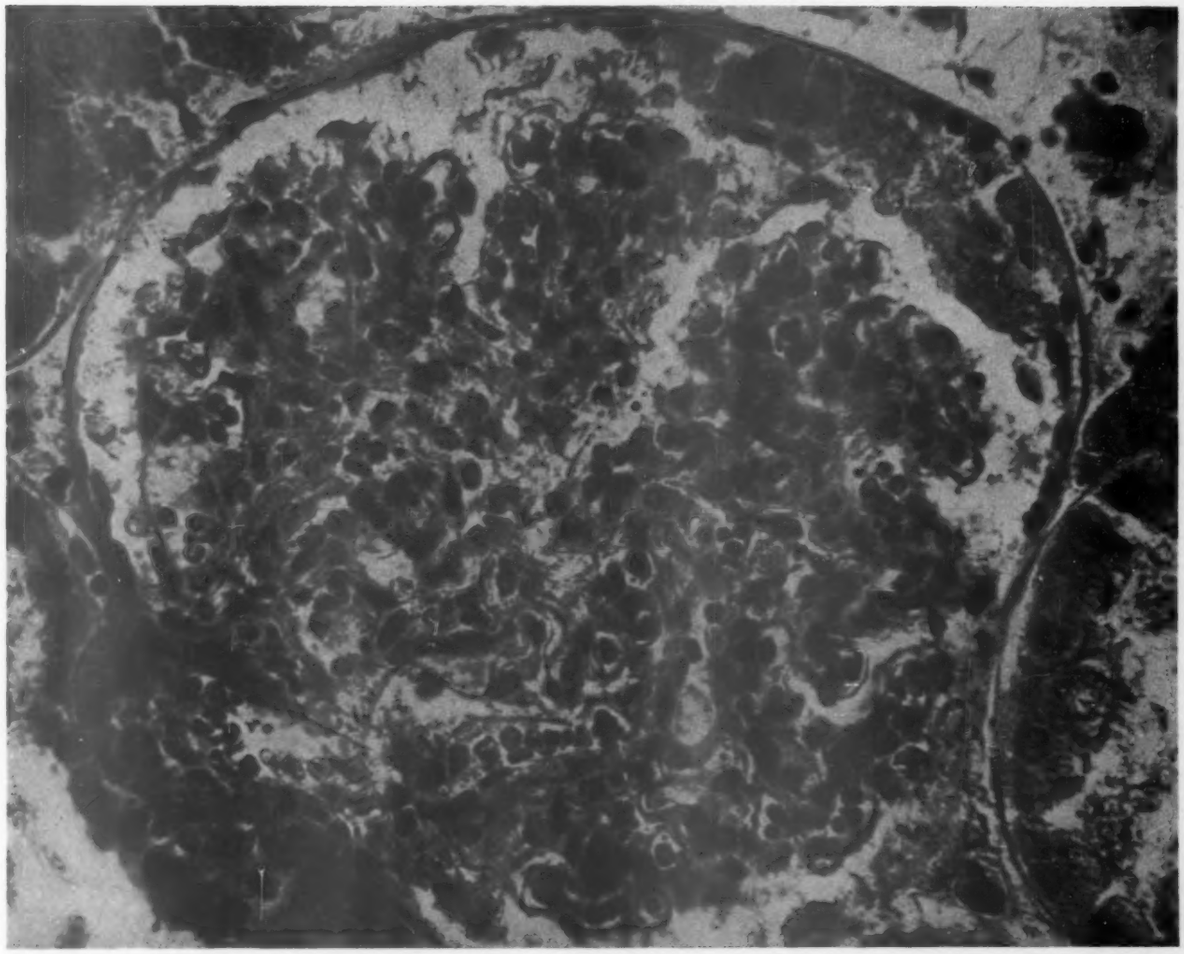

FIG. 7. Case IV. Note the increased cellularity of the glomerular tuft, the swollen capsular cells and the debris in Bowman's space. Hematoxylin and eosin; original magnification, × 1080.

sive," and recurring episodes of nausea and vomiting. She lost weight and tired easily. Two weeks after admission to that hospital she had one episode of epistaxis, puffiness of the face and complained of pain in chewing and swallowing. These symptoms subsided.

The laboratory data (reported from patient's local hospital) on October 30, 1944 showed white blood count 12,500; differential: polymorphonuclear leukocytes 86 per cent, with 78 per cent segmented forms and 8 per cent stab forms, lymphocytes 14 per cent. The hemoglobin was 18.0 gm./100 ml. and the red blood count 4.7 million per mm.^{3} Urinalysis on October 30 showed specific gravity 1.030, 0.02 gm. albumin/100 cc., numerous white blood cells per high power field and 100 red blood cells with some clumps per high power field. There was albuminuria up to 0.05 gm./100 cc., granular casts, blood and pus cells on repeated urinalysis. The serum nonprotein nitrogen on November 2 was 44 mg. per cent. Typhoid, paratyphoid and undulant fever agglutinations were reported as negative. A blood culture showed no growth.

Three days after the patient was discharged from the local hospital she had a "black-out" spell. The details of the black-out spell were lacking. She was admitted to the Mary Hitchcock Memorial Hospital.

Physical examination on admission showed temperature 98.6°F., pulse 120, respirations 20, blood pressure 90/50. She was obese, pale and anxious. Positive findings included bloody crusts in both nares, several decubitus ulcers, bilateral flank tenderness, a poor quality to the heart sounds, mottled extremities and diminished dorsiflexion of the feet. The liver was not palpated.

The white blood count was 9,650; differential: polymorphonuclear leukocytes 78 per cent, stab forms 1 per cent, lymphocytes 15 per cent, monocytes 2 per cent and eosinophils 4 per cent. The sedimentation rate was 35 mm./hr. The hemoglobin was 9.8 gm./100 ml., and the red blood count 3.43 million

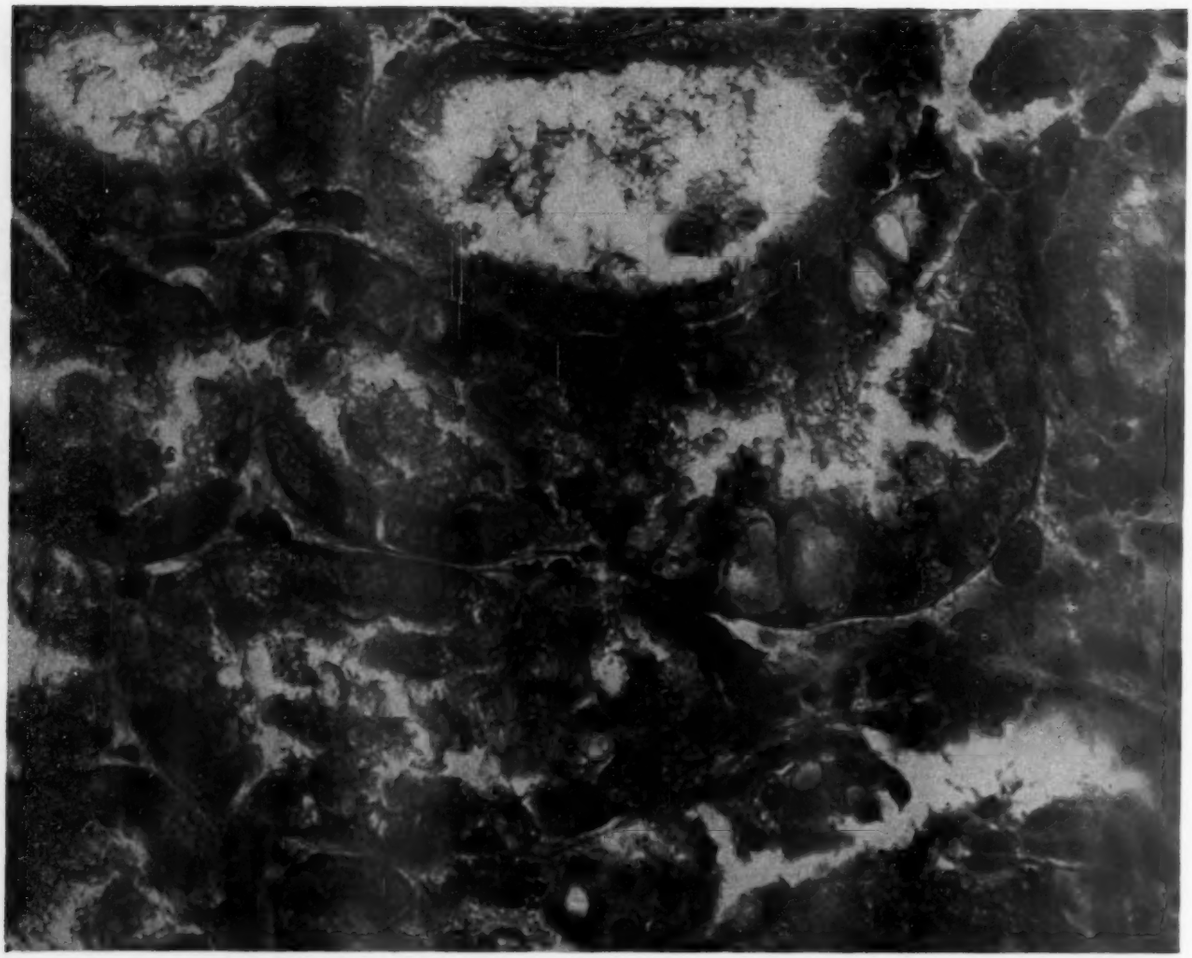

FIG. 8. Case IV. The tubular epithelium exhibits marked vacuolization. Hematoxylin and eosin; original magnification, × 870.

TABLE IV

Date	Serum Total Protein (gm./ 100 cc.)	Serum Albumin (gm./ 100 cc.)	Serum Globulin (gm./ 100 cc.)
12/18/44	5.3	2.7	2.6
12/27/44	5.7	1.5	4.2
1/8/45	6.1	2.2	3.9

per mm.^{3} Urinalysis: Specific gravity 1.011, albumin 0.1 gm./100 cc., 100 white blood cells per 10 high power field, 300 red blood cells per 10 high power field, no casts. The serum nonprotein nitrogen was 35 mg. per cent. Serum protein values appear in Table IV.

No pathogens were found in the feces. Serologic tests for syphilis gave negative results. A skin test for trichinella done during the third month of her illness was negative.

The patient's early hospital period was characterized by nausea, occasional vomiting, diarrhea and fever ranging from 100°F. to 101°F. By the twelfth hospital day marked hepatosplenomegaly and an anal fistula developed in the patient. It was thought that the hepatomegaly was due, in part, to congestive heart failure and digitalis was administered. However, there was little improvement. Therapy consisted of a low fat, high caloric diet, supplemented with vitamins and intravenous amino acids.

On continued supportive therapy the patient made fair progress until the sixth hospital week when, on February 1, 1945, a nasal septum perforation accompanied by profuse epistaxis occurred. Following nasal packing a purulent left-sided otitis media developed. Cultures of the throat and drainage from the ear grew predominantly beta hemolytic streptococci. The patient was treated with penicillin and the otitis subsided. During this period there was no significant change in the urine which had regularly shown albuminuria, red cells and pus cells. On February 17, the patient was discharged for further convalescence at home.

FIG. 9. Case V. There is marked distortion of the liver parenchyma by broad bands of connective tissue. Note the severe fatty change of the liver cells. Hematoxylin and eosin; original magnification, × 210.

She was readmitted to Mary Hitchcock Hospital on February 20, 1945. The father gave the history that shortly after arriving home the patient complained of abdominal pain and by the next day generalized muscle pains and restlessness culminating in delirium. had developed. On admission she was semicomatose and in extremis. There were numerous petechial hemorrhages and purpuric areas, a tachycardia, distention of the abdomen with obvious ascites and an enlarged liver. The white blood count was 46,250; differential: polymorphonuclear leukocytes 70 per cent, stab forms 16 per cent, lymphocytes 14 per cent. The hemoglobin was 10.1 gm./100 ml., serum nonprotein nitrogen 46 mg. per cent, total proteins 5.1 gm. per cent, albumin 1.6 gm. per cent, globulin 3.5 gm. per cent. On the day following admission the patient's respirations were weak and rapid. She died on February 21, 1945, at 1:40 A.M. An autopsy was performed on February 21 at 11:00 A.M.

Microscopic examination of the diaphragm revealed infiltration of the muscle fibers with eosinophils and lymphocytes. Encysted trichinae surrounded by eosinophils, polymorphonuclear leukocytes, lymphocytes and macrophages were found. The cysts were not calcified. One section revealed a trichinella larva within the lumen of a capillary.

The liver weighed 2,100 gm. The external surface was slightly granular and yellow with scattered areas of purple mottling. The cut surface was similar in appearance. There was loss of lobular markings. On microscopic examination (Fig. 9) the normal architecture was found to be completely destroyed, with bands of connective tissue dividing the liver cells into irregular lobules varying in size and without relationship to the central vein. The connective tissue bands contained lymphocytes and plasma cells. In a few areas there was an increased number of immature biliary ducts. The parenchymal cells showed marked fatty change. Droplets in the cytoplasm were shown to be positive for neutral fats by scharlach R stain. There was slight liver cell regeneration.

Each kidney weighed 175 gm. The capsules stripped

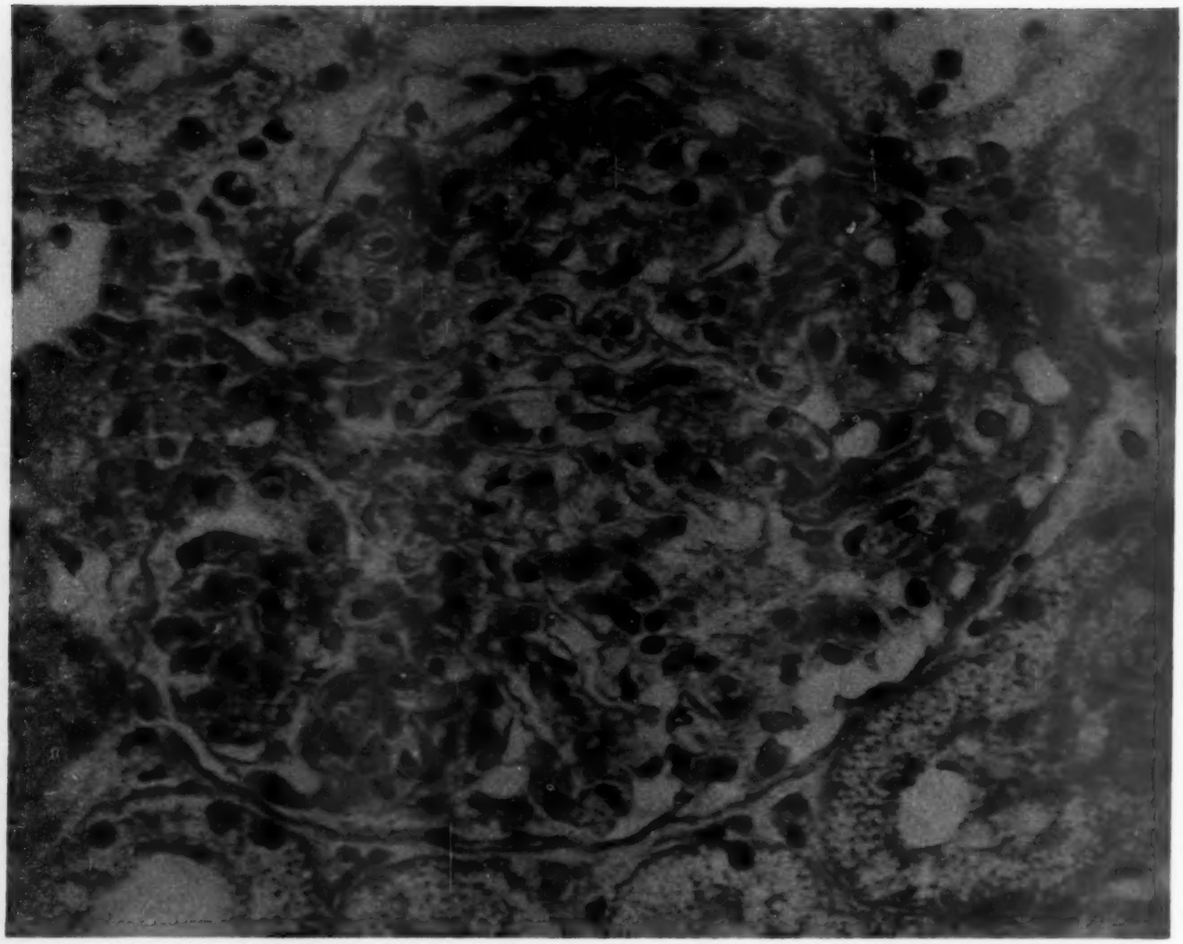

FIG. 10. Case v. Note the swollen appearance of the glomerular tuft. There is increased cellularity and infiltration by polymorphonuclear leukocytes. Hematoxylin and eosin; original magnification × 1080.

with ease revealing a smooth red-brown surface containing numerous petechiae. On cut section the markings of the cortex and medulla were indistinct. Scattered throughout the medulla and pelvis were numerous petechiae. Microscopic examination (Figs. 10 and 11) disclosed swollen glomeruli and increased cellularity due to proliferation of the endothelial cells and infiltration by polymorphonuclear leukocytes. In some of the glomeruli there were small focal areas of necrosis as demonstrated by loss of cellular structure and deposition of fibrin. Some of the glomeruli were filled with red blood cells, many of which had extended into the capsular space. The capsular space in other areas contained a pink granular material and polymorphonuclear leukocytes. Bowman's capsule showed swollen epithelial cells. The tubule epithelium in the proximal and distal tubules showed moderate to marked vacuolization. Scharlach R. stain of the tubular epithelium was positive for neutral fats. The lumen of the tubules, including the collecting tubules, contained a pink granular material and polymorphonuclear leukocytes. There was an occasional focal deposit of calcium salts in the lumen of some of the collecting tubules.

Other necropsy findings were myocarditis, bronchopneumonia and ascites.

COMMENTS

Hepatic abnormalities in trichinosis have been reported in the past. Cohnheim[2] was one of the first to do so. He described the autopsy findings in a twenty-two year old girl who died of trichinosis in whom he found a saffron- to ochre-colored, markedly enlarged liver with isolated small hemorrhages throughout the parenchyma. On microscopic examination he observed uniform fatty degeneration which he likened to that seen in the severest form of phosphorus poisoning. Others[3] have observed fatty degeneration at necropsy. Frothingham[4] reported an autopsy from the Boston City Hospital in which he found

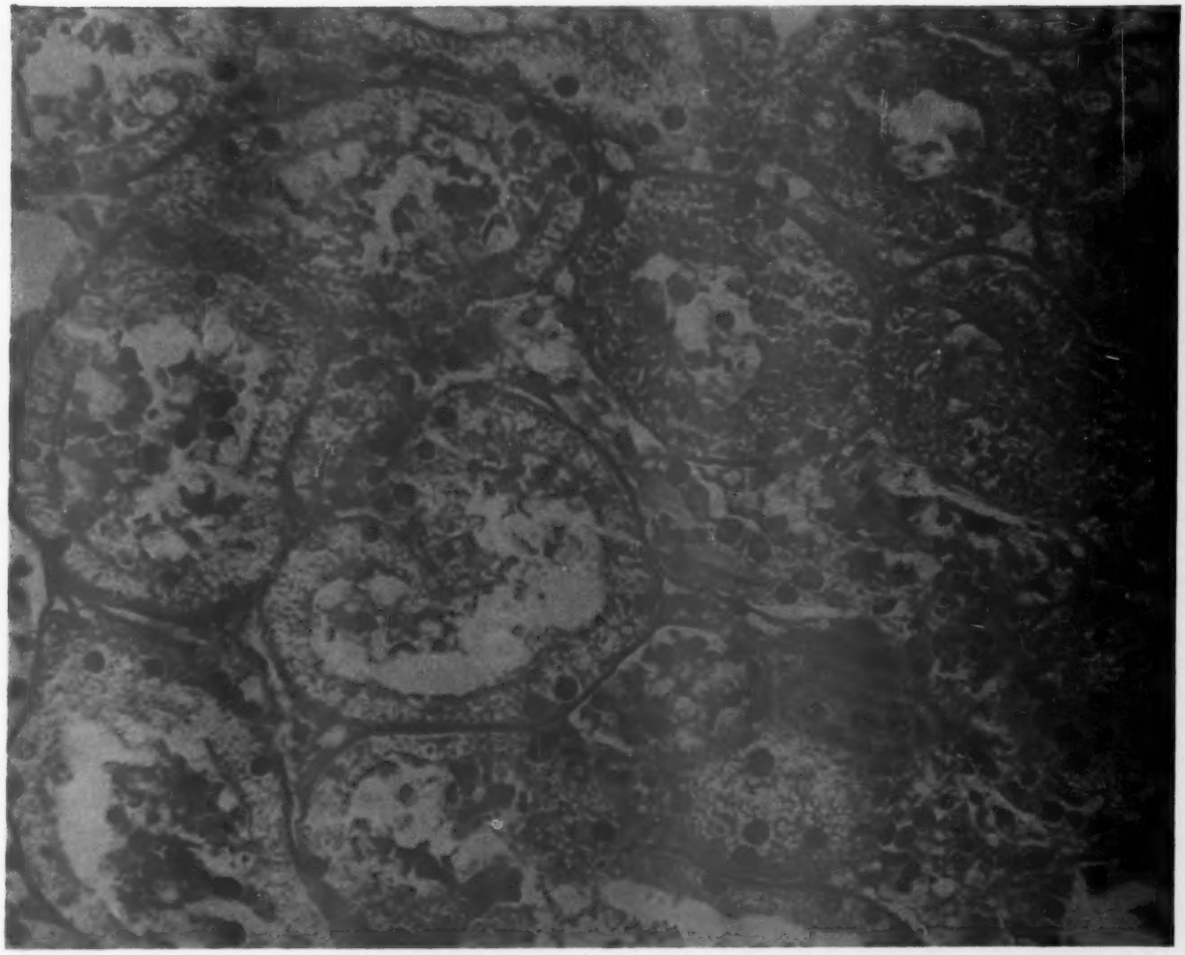

FIG. 11. Case V. The tubular epithelium shows marked granularity with moderate vacuolization. The lumina contain granular debris, lymphocytes and polymorphonuclear leukocytes. Hematoxylin and eosin; original magnification, × 930.

a larva outside a vessel in an area of parenchymal necrosis and a larva in a sinusoid with no apparent surrounding reaction. He also described the presence of fat in the outer half of the lobules. Clinical observations on liver involvement are more rare. Ferrer[5] gave a limited report of a case proved to be trichinosis in which the urine showed a marked diazo reaction early in the course of the disease in the presence of hepatosplenomegaly. However, jaundice is an extremely rare finding in the disease. Dammin[6] was one of the first to present liver data. He also reported the finding of larvae in the arterial blood. It remained for Kushlan[7] to present the first detailed study of a case in which serial liver function data were obtained. The case, however, was complicated by the presence of a prostatic carcinoma and hepatic metastasis was not ruled out. An autopsy was not performed. Roehm[8] reported a case in which there was an abnormal cephalin flocculation test, an elevated thymol turbidity and a high serum cholesterol ester fraction.

Liver studies were carried out in our first three patients. All three showed an abnormal retention of bromsulfalein. This was most marked and persisted longest in Case I. In Case II the bromsulfalein test was found abnormal sixteen days after onset of the initial symptoms. Clinically there was nothing at that time to suggest liver disease. The bromsulfalein test was not done in Case III until the sixty-seventh hospital day, or nearly one hundred days after the onset of illness. The results of the thymol turbidity test were abnormal in Cases I and III and normal in Case II. The percentage of cholesterol esters was abnormal on the fiftieth hospital day in Case III. The cephalin floccula-

tion test was normal in Cases I, II and III. No liver function studies were done in Cases IV and V.

The serum protein values are of special interest. A decrease in total serum proteins, primarily in the albumin fraction, was observed relatively early in all four cases in which serum protein determinations were obtained. Marked hypoalbuminemia and slight increase in the globulins were noted in Cases III and V. Hanes[9] described trichinosis in a twenty-three year old woman in whom severe hypoalbuminemia associated with anasarca was obsered. Kushlan's and Roehm's patients were hypoalbuminemic. Functional or pathologic evidence of liver damage was noted in all our cases of protein derangements. Dietary deficiencies are known to produce liver injury. It is clear from the case reports that maintaining the general nutrition of patients with severe trichinosis is a major problem. All our patients had marked anorexia and did not feel like eating, particularly in the early stages of disease. Nausea, vomiting and diarrhea may be protracted, as demonstrated in Cases IV and V, and to a lesser degree, in Case I. There is little information on absorption from the gastrointestinal tract during a protracted infection and malabsorption may be a factor. Dietary deficiency is usually most severe prior to entering the hospital. Probably the reason changes in serum proteins have not been observed in the past is that they have not been looked for. Albuminuria occurs frequently but is not severe enough in recorded cases to produce protein depletion. Protein needs for repair must be enormous in cases in which there is generalized muscle and visceral invasion and destruction by the larvae. It is also of interest to speculate that nebulous allergic factors may play a significant role in the production of hepatic damage and interference with normal protein metabolism.

The liver abnormalities demonstrated in Cases IV and V are important. The LeC. family unwittingly provided a human experiment in the study of the development of this disease in the liver. All members of the family were infected at the same time and received essentially the same care. The three female members of the family died at different stages of the disease, providing an opportunity to study the progression of changes. The mother died ten days after the onset of symptoms. Unfortunately, tissue autolysis made her postmortem study of limited value except to note that there was no significant fatty change in the parenchymal cells of the liver. A. LeC. died on the fifty-fifth day and a severe degree of fatty change was observed in the parenchymal cells with the greatest damage to the cells in the periportal or peripheral portion of the liver lobule. Early connective tissue changes were also seen. P. LeC. died 126 days after the onset of the disease; portal cirrhosis, portal hypertension and ascites had developed and the patient died in liver failure. Frothingham's patient died twenty-six days after the onset of symptoms and fatty changes were limited to the outer half of the liver lobules.

From these case reports and comments it is clear that a number of factors were involved in producing the severe degree of liver damage observed. Such factors include: (1) poor nutrition aggravated by persistent gastrointestinal tract symptoms such as vomiting and diarrhea; (2) direct liver invasion by the trichinae larvae with associated inflammatory reaction; (3) vascular damage, primarily capillary; (4) other, such as allergic factors and the like, which are thus far undetermined. It is worthwhile to reemphasize that liver injury may occur soon after the initial invasion by the larvae and that a long debilitating course of illness may lead to irreversible liver damage. The serial changes observed in Cases IV and V are consistent with Himsworth's[10] concepts of the liver's response to injury, and to our knowledge represent the first such series of cases in humans. It is interesting to ponder the survival of the male members of the family. One doubts that their fortunate outcome was entirely related to the number of trichinella larvae ingested although that may be the major factor.

Renal changes in trichinosis have been described in the literature. Cohnheim described the kidneys in his case as being of normal size with a smooth yellow surface. On cut section the parenchyma was soft, the cortex thick and intensely dark yellow. Microscopically he described uniform fatty degeneration. Askanazy[11] described occasional fatty degeneration of the epithelium, tubular necrosis and hyaline casts in persons and animals with trichinosis. Frothingham reported intracapsular, intratubular and interstitial edema and congestion of the pyramidal vessels. Van Cott and Lintz[12] reported "acute diffuse nephritis" in a twenty-seven year old person who died four weeks after onset of symptoms, and amyloid degeneration of the kidneys in a twenty-one-year old girl who

died in the eighth week of infection. However, the data presented were sparse in both clinical and pathologic detail. Cummins and Carson[13] give a necropsy report of "acute parenchymatous nephritis" in a fatal case. In the same case there was an infarct at the inferior pole of the right kidney. Details were lacking. Reimann, Price and Herbut[14] reported two cases of trichinosis in which vascular changes suggesting periarteritis nodosa were noted. Renal insufficiency developed in both of these patients. The second patient died and autopsy findings revealed changes consistent with chronic glomerulonephritis. However, one cannot be certain that this patient had no antecedent renal damage. Yesner[15] has recently reported on the renal Shwartzman phenomenon in trichinosis.

Clinically, trichinosis is often initially diagnosed as nephritis. A great many case reports in the literature show abnormal urinary findings as evidenced by albuminuria, hematuria, granular and hyaline casts. All our cases except Case I showed definite urinary abnormalities. Case II was most striking. The serum nonprotein nitrogen was elevated to 95 mg. per cent on admission and renal function tests performed early in the hospital course showed marked depression in the urea clearance and the phenolsulfonphthalein excretion. The serum nonprotein nitrogen returned to normal limits by the fiftieth hospital day and the urea clearance returned to within normal limits by the hundredth hospital day. However, renal clearance data obtained one year after discharge showed a depressed glomerular filtration rate and decreased renal blood flow. The interpretation of the nephritis in this case is clouded by history of a streptococcal infection prior to hospital admission. An antistreptolysin titer on the fourth hospital day was significantly elevated and on one occasion shortly after admission beta hemolytic streptococci were cultured from the pharynx. Therefore, the possibility of a primary coexisting glomerulonephritis following a streptococcus infection cannot be ruled out.

Cases IV and V showed elevation of the blood urea nitrogen, albuminuria and hematuria. No renal function studies were carried out. The postmortem kidney findings in these two cases are described in the case reports. Both glomerular and tubular damage may occur. Evaluation of the findings in Case V must also be modified by the fact that three weeks before death the patient developed an acute otitis media caused by the beta hemolytic streptococcus. This infection was promptly treated with penicillin. However, there was clearcut evidence that this patient had urinary abnormalities for one hundred days prior to the acute otitis media. It is not easy to list or to explain all the factors which cause renal abnormalities. We have found no report in which trichinella larvae have been observed in the kidney. Certainly, capillary vascular damage plays a significant role but how the vascular damage occurs is not clear. Allergic phenomena may be implicated. Such speculation can only await basic investigation.

There is no specific therapy for trichinosis. The cases herein cited illustrate the importance of a rigid program of care in severe cases of trichinosis. This care includes maintenance of adequate nutrition, alertness to possible intercurrent infections and to the possible diffuse nature of the disease, and provision of proper follow-up. ACTH and cortisone have been used with varying success in trichinosis. One cannot draw definite conclusions from cases reported. Two of our severely ill patients received aspirin on a four-hour schedule with apparent satisfactory response. The specific role of aspirin is not clear.

SUMMARY

1. Five cases of trichinosis are presented which illustrate hepatic and renal dysfunction and anatomic changes in this disorder.

2. Hepatic dysfunction is manifested by abnormal liver function tests. There was reduction in bromsulfalein excretion in all our patients; this test may become abnormal as early as sixteen days after the onset of symptoms.

3. The hepatic changes may include: direct invasion of the liver sinusoids by the trichinella larvae; fatty changes and degeneration, particularly involving the peripheral zone of the liver lobule early in the course of the disease; progression to frank cirrhosis in one case.

4. Hypoalbuminemia was a prominent feature of four of the five cases presented. The possible factors and significance of the hypoalbuminemia are discussed.

5. Nephritis occurred in three of the five cases presented. The functional and pathologic data are reported. The damage may be both glomerular and tubular. The disease may simulate acute and chronic glomerulonephritis.

6. Trichinosis in its severe form is a diffuse disease involving widespread vascular damage,

widespread tissue invasion and multiple organ damage.

7. The therapeutic significance of our experience is briefly discussed. The use of salicylates bears further investigation.

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Review

Hyperparathyroidism*

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DURING the past thirty years since the first successful removal of a parathyroid adenoma for hyperparathyroidism[17] the clinical and pathologic features, and the hormonal and chemical dynamics of this entity have been outlined and developed in several reviews from both American and European centers,[1,4,14,24] yet this is a relatively "young" disorder on the medical scene and its many vagaries and subtleties are still completely to be recorded. At Duke Hospital during the past twenty-five years twenty-seven cases of hyperparathyroidism have been recognized. During the first twenty-four years seventeen cases were diagnosed; during 1954 and 1955 ten more cases were observed. It was this recent intensive experience that prompted us to initiate a study of the entire group of twenty-seven cases, and to attempt to learn what has served as the basis for this more frequent recognition. It is the purpose of this report to summarize that review and to document particularly certain features of several of our cases that previously have been commented upon in the literature either infrequently or not at all.

General Character of Series. The inclusion of a case in this series depended upon finding a parathyroid adenoma at operation (nineteen cases) or at autopsy (six cases), or upon a combination of clinical and blood chemical findings that make the diagnosis almost certain (two cases). Four of the autopsied cases were correctly diagnosed antemortem; the two that were not are of special interest and later are referred to in some detail.

Eighteen cases occurred in women, this sex predominance being similar to all other large series reported except the group cited by Reinhoff in which fourteen of the twenty-seven cases were in men.[21] Most cases were in the forty to sixty years age group (twenty cases), the entire range being between thirteen and sixty-nine years. There were no instances of multiple adenomas or of generalized hyperplasia[22] included in this group. In two patients the adenomas were located in the mediastinum, a frequency comparable to the more extensive experience of Black.[4]

TABLE I
CLINICAL CLASSIFICATION ACCORDING TO CRITERIA OF ALBRIGHT[1]

Group	No.
Renal disease only	12
Bone disease only	2
Both renal and bone disease	9
Neither renal nor bone disease	4

The usual clinical classification of hyperparathyroid cases along the lines outlined by Albright[1] into patients with either (1) renal manifestations only, (2) bone disease only, (3) both renal and bone disease and (4) neither renal nor bone manifestation but signs and symptoms related to hypercalcemia *per se*, has been applied here and is listed in Table I. Table II summarizes chronologically the clinical and chemical characteristics of the entire series of twenty-seven cases.

Symptoms and Duration of Symptoms. It has been repeatedly emphasized that the symptoms referable to this disorder can be either singularly characteristic and direct or extremely diverse and perplexing. The simplest complex is that of

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TABLE II

TWENTY-SEVEN CASES OF HYPERPARATHYROIDISM (DUKE HOSPITAL, 1930–1955)
CLINICAL AND BIOCHEMICAL CHARACTERISTICS

Case No. and Patients	Age and Sex	Date Diagnosed	Confirmed By	Duration of Stone History (yr.)	Bone Status	Gastro-intestinal Involvement	Range of Values	
							Serum Calcium	Serum Phosphorus (mg. %)
1, N. B.	47, F	11/35	Operation	15	Porotic	Constipation	14.1–15.3	1.2–2.1
2, H. D.	44, F	12/35	Operation	Dx by x-ray	Moderate	Constipation	15.4–18.9	2.0–3.0
3, J. N.	34, M	8/36	Operation	.....	Moderate	Anorexia	13.3–14.8	2.3–4.0
4, A. App.	49, F	9/37	Autopsy	5	Moderate	Weight loss	21.0–22.0	4.7–4.8
5, N. T.	46, F	3/38	Operation	10	.....	.....	13.6–13.7	1.4–2.5
6, E. S.	49, F	4/38	Operation	17	Moderate	.....	14.4–15.0	3.5–4.3
7, E. Jo.	54, F	8/38	Autopsy	20	.....	Weight loss	14.0–14.5	3.6–3.7
8, B. S.	53, F	9/38	Operation	.....	Marked	Weight loss	11.5–12.5	2.5–3.8
9, V. S.	57, F	11/38	Operation	3	Moderate	Marked	14.3–19.8	1.5–5.5
10, E. T.	35, M	9/45	Operation	Dx by x-ray	Marked	Marked	12.5–17.7	2.0–3.8
11, M. T.	53, F	1/47	Clinical	10	Moderate	Moderate	13.7–13.9	2.5–3.9
12, H. A.	69, M	2/49	Autopsy	.....	.....	.....	.....	.....
13, D. S.	15, M	1/50	Autopsy	.....	.....	Marked	.....	.....
14, N. R.	39, F	8/50	Operation	15	Moderate	.....	10.6–11.3	2.4–2.6
15, W. W.	13, M	7/52	Operation	3	.....	Anorexia	12.9–15.5	3.0–3.1
16, B. N.	48, F	7/53	Operation	20	.....	.....	11.8–13.5	2.4–3.5
17, W. McD.	44, M	8/53	Autopsy	.....	.....	.....	10.5–10.8	8.8
18, E. Ja.	42, F	4/2/54*	Operation	1½	.....	.....	11.2–17.2	1.9–2.5
19, S. B.	48, F	4/12/54	Operation	3	.....	.....	8.5–13.9	1.8–3.6
20, A. And.	55, F	9/7/54	Operation	.....	Slight	Marked	10.0–15.4	2.4–2.9
21, W. M.	52, F	9/27/54	Operation	28	.....	Slight	10.6–11.3	2.2–2.7
22, D. N.	50, F	10/18/54	Autopsy	15	.....	Moderate	8.7–11.8	2.5–9.3
23, B. L.	59, F	10/26/54	Operation	15	Slight	.....	11.6–14.5	1.8–3.8
24, J. H.	46, M	11/29/54	Operation	12	Slight	Marked	16.7–19.0	2.3–3.2
25, S. S.	61, F	1/10/55	Operation	18	.....	.....	10.8–11.6	2.5–2.9
26, W. McG.	45, M	1/20/55†	Clinical	10	.....	.....	9.2–11.0	1.8–5.1
27, N. W.	49, M	5/12/55	Operation	.....	.....	Marked	8.8–11.2	1.8–3.1

* Date parathyroid adenoma was demonstrated.
† Date clinical diagnosis was mentioned.

symptoms referable to nephrolithiasis (such as renal colic, hematuria or "passing sand") or to bone disease (insidious fracture, deep aching back pain, bone mass). It is from such cases that a reasonably accurate index to the duration of this disorder can be gauged. Several authors have indicated that hyperparathyroidism can be a disease of prolonged duration.

The disease was estimated to have been present for thirty-nine years in Case 10 of Albright's first clinical review.[1] When this patient was seen at the Massachusetts General Hospital, at the age of fifty-four, she was treated for a urinary bladder stone that had developed in a cord bladder. The cord bladder was the result of a vertebral fracture incurred at the age of fifteen years when she had lifted a heavy object. It was Albright's thesis that the vertebral fracture represented altered bone metabolism at that early age, and thereby was the primary manifestation of a parathyroid adenoma found thirty-nine years later during evaluation for the bladder stone.

Hellstrom[12] has listed one case of a sixty-two year old woman, who had a history of renal involvement alone, as having had symptoms of her disease for thirty-one years. Black[4] mentions two cases in the Mayo series with histories of renal colic for thirty-two and twenty-seven years. In a later paper Hellstrom[14] estimates that in his total experience of fifty cases the average duration of symptoms was eight years; eleven of these patients are listed as having had symptoms for more than fifteen years, four patients with symptoms for over twenty years.

In our series we are impressed by the long-

term histories, particularly in those eighteen patients with renal manifestations as the primary symptomatic feature of their disease. In this group of patients the average duration of symptoms is twelve years, the range being between one and one-half and twenty-eight years. Five patients had symptoms for six years or less, ten patients had symptoms from nine to eighteen years and three patients had symptoms for eighteen years or more.

There are two major reasons for emphasizing the long-term chronic character of this disease: (1) to point out that we must become sufficiently alerted to this entity so as to establish the diagnosis earlier and (2) to indicate that extremely long histories are of themselves a point in favor of the diagnosis of hyperparathyroidism. Despite the occasional and dramatic instance of acute parathyrotoxicosis (two cases in this series), this is essentially a chronic illness.

CASE 21. W. M., a fifty-two year old white woman, experienced the first episode of right renal colic at age twenty-four. Four years later she had her second attack, and at this time passed a stone. In the ensuing five years she had several episodes of renal colic bilaterally and was first admitted to Duke Hospital at the age of thirty-five. Calculi on the right were visualized by x-ray. The serum calcium was 10.6 mg. per cent and the serum phosphorus 2.2 mg. per cent. (These values were not interpreted as being abnormal at this time.) The following year a right ureterolithotomy was performed. The patient continued to have attacks of colic, fever and hematuria, and thirteen years later left nephrectomy was performed at another hospital for recurrent stones and infection. Two years later symptoms of dull, aching upper abdominal pain developed, associated with anorexia, nausea and vomiting. During the six months preceding admission to the hospital the patient lost twenty pounds in weight. Physical examination revealed evidence of recent weight loss only. X-ray studies demonstrated a stone in the right kidney area; the bones exhibited only a slight decrease in density. The gastrointestinal x-ray series was normal. Serum calcium levels were 11.0, 11.3 and 11.0 mg. per cent, and serum phosphorus 2.6, 2.7 and 2.7 mg. per cent. Because of the history and blood chemical finding, neck exploration was carried out and a parathyroid adenoma removed. The patient has since done well and reports a sense of well-being, including increased auditory acuity[5] which she had not experienced "for a great many years."

Whereas the first cases of hyperparathyroidism were primarily instances of severe bone involvement (Mandl's case, Dubois' Captain Martel), this facet of the disease is becoming less prominent and in recent years emphasis has been on finding cases among persons with renal stones. In 1948 Albright wrote, "about five per cent of all patients with kidney stones in Boston have underlying hyperparathyroidism as its cause."[24] In 1950 from their urology clinic Beard and Goodyear demonstrated parathyroid adenoma in 5 per cent of their patients with urinary tract lithiasis.[2] In our experience at Duke this pattern of emphasis has also evolved, although on a much more limited scale. Eight of the first eleven patients (1935 to 1947 period) had bone disease as a prominent aspect, but during the past eight years we have had no cases of true osteitis fibrosa generalisata. Of the three cases diagnosed clinically during the 1947 to 1954 period, all had predominantly renal colic as the presenting symptom. During this past year, although renal lithiasis has been important in directing clinical thought, we have begun to focus more attention on the type of case in which neither renal nor bone symptoms are prominent. In this category there are those cases in which either the central nervous system or the gastrointestinal tract, or the peripheral vascular tree are primarily symptomatic. Finally there is that instance when symptoms implicating all of these systems presents a diffuse involvement suggesting the diagnosis of one of the collagen diseases.

Symptoms of the Central Nervous System. Hyperparathyroidism may present as a psychiatric illness. Most recently, Fitz reported two cases of patients whose illnesses were primarily of disturbed mental function,[7] and there are several notations, particularly in case reports of acute parathyrotoxicosis, of marked behavior alterations as part of the disease. In the following case the element of disordered mentation played a prominent role, although there were many accompanying disturbances. A segment of this patient's illness might be termed an example of "parathyroid psychosis."

CASE 20. A. A., a fifty-eight year old white woman, entered with the chief complaint of abdominal pain. Two months prior to admission she complained of vague discomfort in the upper abdomen, anorexia and constipation. She experienced many "crying spells." During the week prior to admission she remained in bed complaining of weakness and "nervousness." The family reported that over the past ten years, following the death of the patient's husband, she had been relatively inactive, doing only minor household tasks in her son's home. She was always considered to be a

"quiet" person but appeared to have become more withdrawn during the week prior to admission.

On admission she appeared pale and chronically ill and complained bitterly of upper abdominal discomfort. The blood pressure was 165/95. The remainder of the physical examination was essentially unremarkable. Accessory clinical findings were as follows: hematocrit 33 per cent; white blood count 5,200/mm.^{3} with a normal differential; all other findings including urinalysis, serologic reactions for syphilis, blood sugar, bromides and non-protein nitrogen were normal.

Shortly after admission the patient became markedly withdrawn, refusing to accept any food or fluids by mouth and crying out from time to time, "Lord, Lord, save me!" To accomplish alimentation a nasogastric tube was passed, and fluid and caloric intake were adequately maintained. Her depression and withdrawal became more marked. She slept irregularly, cried out deliriously most of the day and night. She was transferred to the psychiatric service in anticipation of instituting electroshock therapy. X-rays of the skull and lumbar puncture were normal. Pneumoencephalograms revealed some generalized cerebral atrophy. At this juncture an electrocardiogram was obtained which demonstrated a sino-auricular tachycardia, left axis deviation, and a seemingly short Q-T time with elevated ST segments in V_{1-4} and somewhat peaked T waves. This pattern suggested to one of us (A. H. W.) the possibility of hypercalcemia. The serum calcium was 14.8 and 15.4 mg. per cent, phosphorus 2.4 and 2.5 mg. per cent. Further x-ray studies revealed osteoporosis of the spine. Gastrointestinal series, barium enema and intravenous pyelograms were normal. Twenty-four hour urine calcium excretion, while the patient was on a low calcium intake, was 632 mg.

The psychotic state persisted. Finally, during the fifth week of hospitalization, exploration of the neck was undertaken and a parathyroid adenoma removed. Postoperatively, the patient was noted to have changed dramatically; she inquired as to her whereabouts and expressed an interest in her family for the first time in several weeks. She recalled only vaguely her bizarre and distracted behavior. The serum calcium level fell to 10.7, 9.8, 10.2 and 9.4 mg. per cent; the serum phosphorus gradually rose to 2.9 mg. per cent on the sixth postoperative day. During the postoperative period, the patient's appetite increased and she reported feeling stronger. Upon her return home she resumed limited activities.

Eight months after the operation she was readmitted because of anorexia and weakness. Physical findings were unchanged. All blood chemical analyses were normal and the psychiatrist found the patient to be minimally depressed, but still markedly improved over her previous admission. The family felt that her mental status had returned to a level that she had demonstrated for many years prior to the recent illness.

Gastrointestinal Symptoms. The gastrointestinal manifestations of hypercalcemia, such as anorexia, nausea, vomiting, abdominal pain and constipation, have often been major features of the history of patients with parathyroid adenomas. This was first emphasized by Gutman and his associates[8] and has been amplified by Rogers and others, particularly in regard to the association of duodenal ulcer with hyperparathyroidism.[22] Black states that of the Mayo series "24% of patients with proved hyperparathyroidism have at the time of examination, or had had in the past, objective evidence of peptic ulcer or had had operations on the stomach presumably because of ulcer. An additional 15 to 20% of patients had some ulcer-like symptoms but an ulcer had never been proved."[4]

Twelve of our twenty-seven patients had gastrointestinal symptoms of severe enough degree to warrant some detailed commentary in the clinical history. One patient (Case 24) had a four-year history characteristic of duodenal ulcer pain and a deformed duodenal bulb was found on x-ray. He was admitted because of severe nausea, vomiting and epigastric pain and, like the patients of Rogers,[22] who pointed out that milk did not agree with them, our patient believed that although milk relieved his abdominal pain, it "somehow makes me feel worse in a little while." The patient also had a twelve-year history of renal colic, and the characteristic blood chemical findings were noted shortly after admission.

Of more tortuous nature, however, is the following case in which the gastrointestinal complaints were prominent but in which a major undercurrent of what was interpreted as a psychoneurotic pattern made the diagnosis of hyperparathyroidism most remarkable and yet not necessarily definitive:

Case 27. N. D. W., a forty-nine year old white man, entered the hospital with the chief complaint of abdominal discomfort and anorexia. The patient had been followed for many years in the outpatient department, having been treated for minor infections, a cerebral concussion and in 1951 for simple fractures of the right fibula and tibia incurred in a fall from a house porch. These fractures had healed well.

He first noted abdominal discomfort two years prior to admission, and anorexia and a 40-pound weight loss had gradually occurred in the ensuing period. The abdominal discomfort was of a deep aching quality in the upper and lower abdomen, occasionally relieved by food. One year prior to admission the patient

noted marked generalized muscle weakness. Six months later he was forced to stop work because of weakness in his right hand. He also noted some low back pain, frequency of urination and nocturia but no episodes of renal colic or hematuria. His family reported that occasionally he was extremely irritable and unreasonable.

On physical examination, he was a thin, active person appearing chronically ill. Blood pressure was 110/70. Other than some minimal weakness of the right wrist, without associated sensory loss, and generalized decrease in muscle mass, there were no unusual findings. Accessory clinical findings were normal except for a variable picture in the gastrointestinal series. In some x-ray films duodenal and antral spasm with possible crater formation was observed, in others the stomach and duodenum appeared perfectly normal. The patient was given a bland diet and tincture of belladonna but this schedule afforded little relief. On psychiatric examination he was thought to be "a passive-aggressive personality, his many complaints and protracted illness affording him an acceptable avenue for his dependent needs." He was discharged and followed in the outpatient department. Because of the vague history of back pain and the suggestive duodenal ulcer further blood chemical studies were carried out. The serum calcium (mg. per cent) levels were as follows: 10.7, 10.4, 11.5, 10.6, 10.3, 11.2; the serum phosphorus (mg. per cent): 1.9, 2.0, 2.5, 2.6. Bone x-rays and intravenous pyelograms were normal. It was finally decided that neck exploration was indicated. A 640 mg. parathyroid adenoma was removed.

Postoperatively the patient noted a definite return of appetite, loss of vague abdominal discomfort, and some return of general strength. Serum calcium values were 9.7 and 9.5 mg. per cent; phosphorus, 3.1 and 3.2 mg. per cent. However, the patient gained only eight pounds within the next three months and did not return to work. He noted increasing weakness and wasting of his hand muscles, and signs of pyramidal tract degeneration developed in his lower extremities. The diagnosis of amyotrophic lateral sclerosis was made (negative lumbar puncture, negative myelogram). The patient once again began to complain of abdominal discomfort, anorexia and weight loss. Because of the duodenal spasm noted in roentgenograms and variability of symptoms suggesting a pancreatic neoplasm, exploratory laparotomy was performed, with no abnormal findings noted. Following this operation the patient has continued to experience symptoms of upper abdominal distress.

Comment: This case illustrates that the character of the gastrointestinal symptoms warranted evaluating the patient's parathyroid function by obtaining serum calcium and phosphorus determinations and, further, that even though chemical indications of hyperparathyroidism were discovered and remedied by surgical removal of the adenoma, the patient's symptoms have persisted and are still unexplained even following exploratory laparotomy.

Vascular Complications. Extensive calcinosis as a consequence of hypercalcemia associated with hyperparathyroidism has been commented upon almost solely as a feature of acute parathyroid intoxication. It was present in the first such case reported[5] and in the case reported from this clinic by Hanes.[10] Both Albright[24] and Black[4] refer to vascular calcification in this regard. Ellis and Barr[6] have reported an extraordinary case of metastasizing carcinoma of the parathyroid gland in which extensive calcinosis was a major feature, producing signs and symptoms of arterial insufficiency of the upper extremities (pulseless, pallid, cyanotic hands) and demonstrating striking calcification of almost all vessels of the extremities on x-ray examination.[6] At postmortem examination the blood vessel walls were heavily infiltrated by calcific deposits, and there were ischemic infarcts in the spleen and lung. Rogers et al.[22] reported a case of a sixty-eight year old man with primary hypertrophy and hyperplasia of the parathyroid glands who was cited specifically for his long history of duodenal ulcer but who for a three-year period had complained of pain in his right foot and leg occasioned by walking. Shortly before his final admission he noted blueness of the great toe of the left foot and demonstrated on examination gangrene of that toe and absent dorsalis pedis and posterior tibial pulses bilaterally. He died in uremia. At postmortem examination there were areas of necrosis and intimal calcification in the wall of almost all large arteries. These changes were believed to be responsible for the gangrene of the foot, and to have derived from the presumed hypercalcemia (serum calcium and phosphorus were not obtained antemortem) attending the hyperplasia of the parathyroid glands.

In light of these experiences it would certainly be reasonable to expect that in certain persons arterial calcification and resulting arterial insufficiency of a peripheral part might be present as a prominent manifestation of a parathyroid adenoma. We believe that the two cases to be described illustrate this clinical variation. In both of these cases the adenomas were uncovered at autopsy, although in the first instance the diagnosis of hyperparathyroidism was suspected on the basis of the serum calcium value. In the second case the presence of a parathyroid adenoma was never suspected, although the remark-

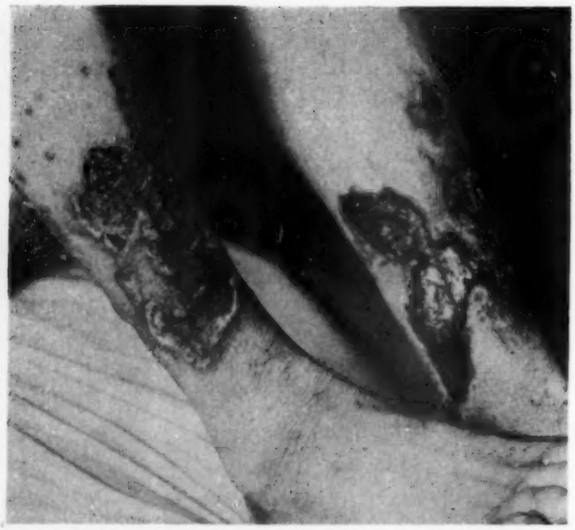

FIG. 1. Large, irregular-margined granulating ulcers on the lower extremities. Case 17.

able calcification of the aorta and bronchial tree seen in the chest x-ray might have served as a reminder if one had thought that hyperparathyroidism can significantly contribute to arterial obliterative disease.

CASE 17. W. McD., a forty-four year old white farmer, entered the hospital with the chief complaint of painful ulcers of the lower legs. One year prior to admission he first noted intermittent arthralgia of the knees, ankles and elbows, accompanied by minimal swelling without local heat or redness. These symptoms gradually subsided but eight months prior to admission were followed by the development of bilateral ankle edema, dyspnea on exertion and one episode of paroxysmal nocturnal dyspnea. The patient consulted his private physician who noted the presence of arterial hypertension. His status remained essentially unchanged until four months prior to admission when bluish black areas developed on the pretibial surfaces of both legs. These areas became exquisitely painful, the pain being made worse by exercise and relieved by rest and the dependent position. The patient also noted deep aching pain in the calves of both legs on exercise. Gradually the pretibial areas broke down and large granulating ulcers developed. On several occasions these ulcers bled profusely following light trauma. The pain became lancinating in quality, prevented sleep and forced the patient to become bedridden. He was admitted to the surgical service for plastic repair of the ulcers. Past history revealed four episodes of renal colic since the age of seventeen years and a brief period, one and one-half years prior to admission, of epigastric pain and distress relieved by food.

Physical examination revealed a pale, chronically ill man. The blood pressure was 165/106. There were large, irregular margined granulating ulcers on both anterior lower legs. (Fig. 1.) Fundi showed an increase in arteriolar light reflex. The heart was enlarged to just beyond the nipple line; A_2 was louder than P_2. Peripheral pulses were well felt at all sites.

Accessory clinical findings were as follows: hemoglobin 8.3 gm. per cent, white blood count, 5,000/cu. mm., red cells were normochromic and normocytic. Urinalysis revealed a specific gravity of 1.002, pH 5.0, trace to 3+ protein (Bence Jones negative), occasional red cells and leukocytes on microscopic examination of the sediment. Serologic tests for syphilis gave negative results; serum non-protein nitrogen was 88 mg. per cent, serum protein 7.2 (4.0/3.2) gm. per cent. Mosenthal test: highest specific gravity was 1.007. X-rays of the chest showed slight cardiac enlargement; lungs were clear and a round calcified mass was noted at the left paratrachial area. Bone marrow showed a decrease in erythroid elements.

During the first three weeks the ulcers were dressed with compresses and were surgically débrided on two occasions. The areas did not heal well, however, and on several occasions bleeding into the dressings was profuse. The patient received multiple transfusions but his general status gradually deteriorated. He became anorexic, transiently confused and disoriented. His serum non-protein nitrogen rose to 224 mg. per cent. At this time serum calcium was 10.8 and 8.8 mg. per cent.* His course was gradually downhill; he became more somnolent and died in his sleep on the twenty-second hospital day.

Biopsy and postmortem findings were as follows: Sections of the skin and underlying tissue removed at the time of débridement revealed areas of epidermal and dermal necrosis and abscess formation. In the dermis and subcutaneous fat there were numerous small arteries and arterioles which showed extensive calcification of the walls, some limited only to the intima, some of the entire wall. (Fig. 2.) Several vessels were occluded by thrombi. At autopsy the remarkable findings were the hyperplastic change of three of the parathyroid glands, and a large calcified left lower pole adenoma many times the size of the other glands. This calcium-rimmed mass was probably what was seen on the x-ray of the chest. The kidneys were somewhat contracted. There were three stones in the calyces on the right. The tubules and glomeruli were reduced in number, scarred and distorted. Interstitial calcific deposits were scattered throughout the medullary areas. The bones revealed widened trabeculae, areas of fibrosis and increased numbers of osteoclasts.

Comment: It might be speculated that the primary disorder was the large parathyroid adenoma, and that nephrocalcinosis and pyelonephritis then ensued leading to the development of the hypertensive dis-

* At this juncture Dr. William L. Sutton, interne on the case, suggested the possibility of hyperparathyroidism.

FIG. 2. Microscopic section of arteriole in the area beneath the leg ulcer (Case 17), demonstrating the calcified intimal layer which appears dark gray in the illustration.

ease. Ulceration of the anterior tibial area in hypertensive vascular disease has been described[15] but in those instances extensive vessel calcification is not specifically mentioned. The serum calcium (10.8 mg. per cent) is definitely higher than is usually observed in parathyroid hyperplasia secondary to renal insufficiency and was in part probably responsible for effecting the arterial calcification and these changes promoted the ischemia of the tissues.

CASE 12. H. A., a sixty-nine year old white farmer, entered the hospital with a history of progressively incapacitating intermittent claudication of the lower extremities for a two-year period. At the onset of the illness he had bilateral ulcers of the lower leg which healed gradually on bedrest. When the patient resumed activity pain recurred and gradually forced him to give up work. During the four months preceding admission to the hospital he experienced pain at rest and for several weeks was unable to sleep without medications. His appetite had decreased and he had lost twenty-five pounds in weight during this time. There was no history of renal lithiasis.

Physical examination revealed a thin, apprehensive man complaining of pain in his legs. The blood pressure was 160/100. Fundi showed narrowing of the arterioles with arteriovenous compression changes. The heart was not enlarged but a harsh grade 3 systolic murmur was heard over the entire precordium, best heard at the apex. The peripheral vessels were firm and tortuous in the upper extremities. The femoral pulses were felt bilaterally, the right popliteal was only faintly palpable, the left popliteal could not be felt at all. Posterior tibial and dorsalis pedis pulses were absent bilaterally. The skin of both feet was cold. The right second toe showed changes characteristic of early gangrene. Neurologic examination was not remarkable.

Accessory clinical findings were as follows: hemoglobin 14.1 mg. per cent; white blood count 12,500/mm.^{3}; differential, normal. Urinalysis revealed a specific gravity of 1.010; protein and sugar were negative and occasional white cells were noted on microscopic examination of the sediment. Serologic tests for syphilis gave negative results. Fasting blood sugar was 100 mg. per cent, non-protein nitrogen

58 mg. per cent, cholesterol 200 mg. per cent, PSP excretion 30 per cent in two hours. Electrocardiogram revealed a left ventricular strain pattern.

The patient was placed on bedrest and given papaverine 60 mg. and demerol® 50 mg. every four hours. This program did not control his pain, and on the fourth hospital day a peripheral nerve crush (the posterior tibial and peroneal nerves) was carried out. Pain was relieved but gangrene of the right foot progressed. On the thirteenth hospital day a right supracondylar amputation was performed. Postoperatively the patient did not do well. The urine output remained low, serum non-protein nitrogen gradually rose to 99 mg. per cent and the patient lapsed into coma. Despite supportive measures he died on the fourteenth postoperative day.

Findings at autopsy were as follows: section of blood vessels of the amputated stump revealed a marked degree of Mönckeberg and atheromatous arteriosclerotic changes. The subendothelial areas contained large masses of fibrous, lipoid, calcific and occasional metaplastic bone tissue. Vessels throughout the remainder of the body revealed marked arteriosclerosis, and intimal and medial calcification. The base of both the mitral and aortic valves was the site of fibrous tissue reaction and striking calcification. Both lower lobe pulmonary arteries contained emboli. The pulmonary arteries throughout showed calcification. The bronchial cartilages were calcified. The kidneys were contracted, scarred, demonstrating the changes of pyelonephritis and in addition, conspicuous calcinosis of the tubular epithelium. In the bones there were areas of fibrosis adjacent to trabeculae, areas of dissolution and conglomerates of osteoclasts. A 600 mg. parathyroid adenoma was noted. The remaining three glands were small and unremarkable.

Multiple System Involvement. Since so many organ systems can be sites of apparent involvement in persons with hyperparathyroidism, if several were to be simultaneously disturbed, the clinical picture might well be confused with entities more frequently associated with multiple system involvement. The following case history is remarkable in that the patient was considered to have a variety of one of the so-called collagen diseases, such as lupus erythematosus, and the downhill course was thought to be the result of renal involvement by that disorder. The appropriate serum chemistry studies were not obtained antemortem but the pathologic findings were unequivocally characteristic of hyperparathyroidism. The insidious development of renal failure in this patient has been the subject of a previous report.[32]

Case 13. D. W., a fifteen year old white boy, first became ill six months prior to admission to Duke Hospital when he noted the onset of nausea and vomiting associated with generalized malaise but without abdominal pain. Because of the persistent character of the symptoms the patient remained in bed for two weeks. After getting up and moving about nausea again developed along with swelling, redness and tenderness of both ankles and stiffness of the hand and wrists. The patient was hospitalized by his private physician who observed the joint swelling and stiffness and found a prolonged P-R interval (0.40) in the electrocardiogram, and a minimal proteinuria. It was his impression that the patient had acute rheumatic fever. The patient was kept in bed and aspirin was administered, with gradual improvement. One month later, however, marked nausea and vomiting and headache again occurred; several days later he experienced an episode in which he suddenly lost consciousness and demonstrated clonicotonic movements of the right hand. Alertness was gradually regained over a four-day period. No residual weakness of the right hand was noted although there was some weakness of the right side of the face. Recovery occurred during the next week but persistent vomiting again developed. The patient had several seizures of the right upper and lower extremities and was found to have a flaccid paralysis of the right arm. He lapsed into a semi-stuporous state. Lumbar puncture was unrevealing. There was some slight rise in the evening temperature in the week preceding admission to Duke Hospital, but no frank chills at any time. There had been a thirty pound weight loss during the five months of the present illness. There was no history of hypertension or known renal disease. During the month prior to admission the patient was severely constipated and required enemas for all bowel movements.

Physical examination revealed a thin, semi-stuporous boy, responding only to painful stimuli. Blood pressure was 180/140 and the pulse 80. Pupils were round and reacted to light; the right was greater than the left. Fundi revealed well outlined nerve heads; vessels were unremarkable and no hemorrhages or exudates were noted. The lungs were clear to percussion and auscultation. The heart was slightly enlarged to the left, with a grade 2 systolic murmur at the apex. No pericardial rub was heard. Extremities showed marked wasting and atrophy of all muscle groups, slightly more marked on right, spindle enlargement of the interphalangeal and wrist area of both hands. Neurologic examination demonstrated hyperactive reflexes on the right, a Babinski response on the right and inconstant right ankle clonus.

Accessory clinical findings were as follows: hemoglobin 12.4 gm. per cent, white blood count 13,900/mm.^{3}, differential unremarkable. The urine was clear, with a specific gravity of 1.008, one plus protein and negative sugar. Serologic tests for syphilis gave negative results. The serum non-protein nitrogen was 65 mg. per cent, total protein 7.4 (4.3/3.1) gm. per

cent, cholesterol 250 mg. per cent, sodium 139 mEq./L., potassium 6.4 mEq./L., chloride 94 mEq./L. Lumbar puncture was clear and pressures normal. Electrocardiogram revealed sinus tachycardia and a P-R interval of 0.20 second. Phenolsulfonphthalein excretion was 12 per cent in six hours. An intravenous benzodioxane test gave a negative result. A biopsy

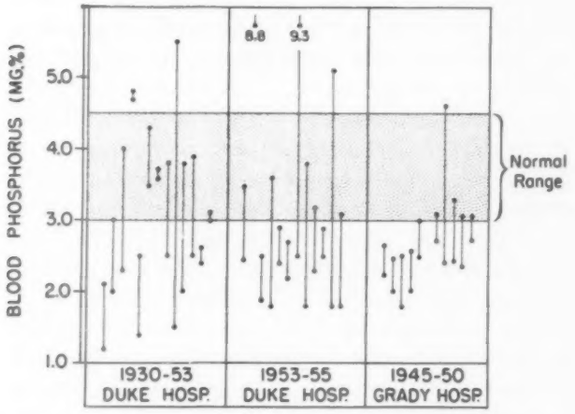

FIG. 3. Blood phosphate levels in patients with parathyroid adenoma during the 1930–1953 and 1953–1955 periods at Duke Hospital and the 1945–1950 period at Grady Hospital[2] demonstrating the consistent occurrence of hypophosphatemia in almost all cases.

specimen of the right deltoid muscle showed only atrophy, vessels were unremarkable. No x-ray studies were performed.

There was some clearing of mentation during the first week of hospitalization but the patient gradually lost ground. His serum non-protein nitrogen progressively rose to 138 mg. per cent. The syndrome of hypertension, athralgia, cerebral vascular disease and progressive renal failure was interpreted as representing a diffuse vascular disease. A course of DOCA and ascorbic acid (used in place of ACTH which was as yet not readily available) was instituted. He was also given tube feedings of rice. His blood pressure gradually fell to 125/70 and then in the last week fell to shock levels. An ulcer of the left cornea developed which rapidly spread into an exudative, necrotizing panophthalmitis. During the last three weeks he remained in a comatose state and on the thirty-second hospital day respirations ceased.

At autopsy the most striking findings were as follows: (1) in the kidneys extensive nephrocalcinosis was found: peritubular, intraluminal and interstitial calcium deposits with several tubules blocked by the calcium casts; (2) in the lungs where, in addition to areas of bronchopneumonia, there was striking calcification of the alveolar walls and cartilages of the bronchi; (3) in the brain where extensive degenerative changes were found in both right and left frontal parietal cortex, although more marked on the left; these changes consisted of focal loss of neurones with histiocytic infiltration and the presence of a small parathyroid adenoma beneath the left lobe of the thyroid gland.

Basis for Diagnosis. Although clinical experience may indicate that hyperparathyroidism

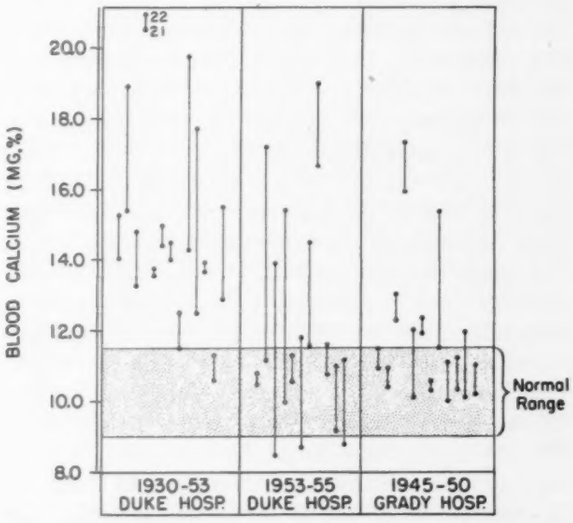

FIG. 4. Blood calcium levels in patients with parathyroid adenoma during the 1930–1953 and 1953–1955 periods at Duke Hospital and the 1945–1950 period at Grady Hospital[2] demonstrating the increasing occurrence of normal or near-normal values in instances of hyperparathyroidism.

should be suspected in many situations far removed from the classic case of osteitis fibrosa generalisata, the ultimate support for such a diagnosis resides in the demonstration of abnormal chemical findings in the blood and/or urine. We believe that we have seen within one year's time such a large proportion of the total experience at this hospital because we have been particularly watchful for those cases of an unusual type and have shifted the emphasis in regard to what chemical changes constitute adequate support for the diagnosis. The previous discussion would indicate that extremely long histories of renal or bladder* lithiasis (patients B. L., S. S., W. M., W. McG.), a complicated psychosis (patient A. A.) and a tortuous emotional and gastrointestinal history (patient

* Although it is difficult to document the details in every case of the more than 600 cases of hyperparathyroidism that have been reported, we believe that aside from Albright's Case 10,[1] already mentioned as a cord bladder with stones, our case (patient W. Mc.G.) with a history solely of recurrent bladder stones and no renal lithiasis is the only such clinical example reported.

N. D. W.) all aided in our looking for this disorder. In the past, chemical confirmation of the diagnosis meant the demonstration primarily of hypercalcemia and hypercalciuria accompanied with hypophosphatemia and elevation of the serum alkaline phosphatase. This latter finding, present only when bone dissolution is prominent, has been encountered rarely in our experience. Since we have done urine calcium determinations in only a few instances, the presence of hypercalciuria has not figured prominently in establishing the diagnosis. We have relied primarily upon the presence of an elevated serum calcium and a depressed serum phosphorus, and in the past year we have particularly emphasized the hypophosphatemia.

Exactly what constitutes an elevated serum calcium and a depressed serum phosphorus depends upon the individual laboratory. The normal range varies from institution to institution and it should be surveyed from time to time in any given laboratory so as to gauge accurately what values are abnormal. In the clinical laboratory at Duke Hospital the method of Tisdall[23] is used for determining serum calcium and the method of Kuttner and Lichtenstein[16] for serum inorganic phosphate determinations. The mean of normal values for calcium is 9.2 ± 0.5 mg. per cent (S. D.) and for phosphorus is 3.4 ± 0.7 mg. per cent. In view of these standards we therefore consider a serum calcium above 10.0 mg. per cent and a fasting serum phosphorus below 3.0 mg. per cent as suspicious. We also believe that a series of values is of more aid in judging the presence of an abnormality, and we usually collect three determinations of each during the observation period.

To illustrate that the demonstration of a depressed serum phosphorus may be more important in making the diagnosis of hyperparathyroidism, we have compared the ranges of the serum calcium and phosphorus values for the cases in the period of 1930 to 1953 and for those in the 1954 to 1955 period. We have also included the values from the Grady Hospital series of Beard and Goodyear[2] collected during the 1945 to 1950 period. Figures 3 and 4 demonstrate this comparison. The "normal range" shaded in the diagrams represents a composite summary of the values listed in several standard textbooks and reference sources.[25–29] The upper limit of normal for serum calcium was 11.5 mg. per cent; the lower limit of normal for serum phosphorus was 3.0 mg. per cent. A cursory glance of both charts will indicate that over the years there has been an increasing occurrence of "normal" serum calcium levels in cases with parathyroid adenoma, whereas the occurrence of "normal" phosphorus levels has probably decreased. During the 1935 to 1953 period all serum calcium determinations were above 10.5 mg. per cent, the most elevated values (21 and 22 mg. per cent) having been found in a case of acute parathyroid intoxication previously reported by Hanes as the first such case in the American literature.[10] During the 1945 to 1950 period at Grady Hospital there were many more serum phosphorus values below 3.0 mg. per cent than there were serum calcium values above 10.0 mg. per cent. During the 1954 to 1955 period at Duke Hospital five of the ten patients had on occasion serum calcium values at or below the 10.0 mg. per cent level. The serum phosphorus values, however, were only rarely above 3.0 mg. per cent (in four patients no value at or above 3.0 mg. per cent was ever obtained) and when elevated were usually associated with some degree of renal impairment (patient D. N., severe pyelonephritis with uremia; patient W. McG., pyelonephritis with Pseudomonas aeruginosa bacteremia and shock, followed by uremia). The consistent occurrence of hypophosphatemia should lead to the consideration of a parathyroid adenoma. Furthermore, we believe that when other causes of a low serum phosphorus have been ruled out and even if the serum calcium is not strikingly elevated, if the clinical picture embodies any of the variations we have previously mentioned, then exploration in search of an adenoma is justified.

A case in point may be cited to indicate how our evaluation of the serum chemical values has shifted:

CASE 19. S. B., a forty-eight year old white woman, was first seen at Duke Hospital in 1946 for epigastric distress, nausea and anorexia. A diagnosis of psychoneurosis was made. She returned in 1951 and was found to have nephrolithiasis. Serum values were as follows (mg. per cent): calcium 11.4, 11.1, 10.9 and 11.7; phosphorus, 2.0, 2.9, 1.8 and 3.2. Our consultation note read as follows: "It is felt that this patient certainly presents a picture which may be compatible with hyperparathyroidism, but that since the laboratory results are only borderline we would defer neck exploration until more definitive evidence is on hand." We believe at this time, in view of our most recent experiences, that we would not hesitate to explore such a patient and would consider the chemi-

cal values cited as good evidence of the presence of hyperparathyroidism.

Since our opinion regarding what constitutes an elevated serum calcium has changed over the years, it was thought advisable to review the most likely source of parathyroid adenomas for cases previously overlooked because of what were considered to have been "normal" serum calcium values. Accordingly all cases charted as "renal lithiasis" in the record library for the period 1950 to 1955 were reviewed. These patients had been seen on a variety of the services of the hospital (medical, general surgical, urologic). Six hundred seventy-two charts were reviewed. Of most interest was the fact that a surprisingly low number had had serum calcium determinations made, only 46 per cent for the entire six-year period. Of those persons so tested, 8.4 per cent were found to have values above 10.5 mg. per cent. Two patients in this group were explored and parathyroid adenomas were removed (they are included in this series). Letters have been sent out to the other patients in this group in whom further evaluation seems indicated, asking them to return for follow-up. To date we have had a disappointing response. It is likely that patients who are not at the moment in appreciable distress would be reluctant to return for further medical study. An encouraging note, however, can be made from this survey in that an apparent accompaniment of our recent interest in hyperparathyroidism has been an increase in the percentage of patients with renal lithiasis in whom serum calcium values were obtained.

Our emphasis on the importance of hypophosphatemia without the concurrence of a remarkable hypercalcemia provides clinical support to the recent enlarging body of evidence that there are probably two and perhaps more[9] types of parathyroid hormones. The two primary hormones are (1) the calcium-mobilizing substance responsible for the dissolution of bone, hypercalcemia and hypercalciuria, and (2) the phosphaturic substance responsible for decreasing renal tubular reabsorption of phosphate, increasing urinary excretion and lowering the serum phosphorus. Munson[19] has reviewed the evidence for the two types of hormones and has described two new technics to assay these activities independently. He has also presented data to indicate that in the process of purifying crude parathyroid extract phosphaturic activity is lost. When equal "calcium-mobilizing" dosages of crude and purified extract are compared, the crude preparation has three to four times greater phosphaturic activity. This would suggest that these two activities are separable and relatively distinct and provides an explanation for the recent failure of many investigators to obtain positive reactions to Ellsworth-Howard tests since purified hormone preparations have been employed. An extension of this work into the clinical realm has led to the speculation that it is possible that parathyroid adenomas may vary as to the type of hormone that is produced (comparable to variations in the type of steroid produced by adrenal cortical tumors) and that in a case such as patient J. H., in whom hypercalcemia and stone formation is prominent, the major hormone produced is the calcium-mobilizing substance, whereas in the case of patient N. W., in whom hypercalcemia was only transient and hypophosphatemia consistent and hyperphosphaturia prominent, the phosphaturic hormone is the major substance elaborated.

Since it is believed that the phosphaturia is a result of decreased renal tubular reabsorption of filtered phosphate, measurement of the renal Tm for phosphate and demonstration of a reduction in this function may be used as a confirmatory diagnostic procedure.[30] This test was carried out in patient N. W. and preoperatively the Tm for phosphate was 78 per cent, postoperatively 95 per cent (normal 91 $\pm$ 4 per cent in our laboratory). Further experiences with this test and various useful modifications will be reported elsewhere.[31]

During the 1954 to 1955 period exploratory operations have been performed on ten persons; tumors were found in eight instances. In the two cases in which no tumor was found, one remains undiagnosed and the other eventually proved to be an example of hypervitaminosis D. *

Postoperative Complication: Acute Pancreatitis. The primary concern of the attending physician during the postoperative period following removal of a parathyroid adenoma has been with the development of tetany and its complications. With improvement in surgical technic, and de-

* This patient was an elderly person who entered in a state of semi-stupor. The history was obtained from the members of the family who were unaware of the vitamin ingestion. It was only postoperatively, some eight or ten days after the last dose of vitamin D that the patient's mental status was clear enough so that the correct history could be obtained.

cline in the incidence of severe bone disease, the development of transient tetany has become less common, and persistent tetany quite rare. The major concern now is with the local effects in the neck and mediastinum. We have, however, encountered one postoperative complication that has been mentioned in the literature twice previously[3,14] and therefore deserves some mention here. This was an instance of acute pancreatitis.

CASE 24. J. H., a forty-six year old Negro laborer, entered the hospital with the chief complaints of nausea, vomiting and back pain. He had had a two-year history of intermittent abdominal pain and progressively more constant nausea and vomiting for a four-month period. There was a twelve-year history of repeated episodes of renal colic and he had had several operative procedures for kidney, pelvic and ureteral stones. Because of the protracted nausea and vomiting there had been a recent weight loss of thirty pounds. The abdominal pain was localized to the epigastrium, unrelated to position, did not radiate to the back and was relieved by food and antacids. Physical examination revealed only the evidence of weight loss in a chronically ill appearing man. The serum calcium ranged between 16.7 and 19.0 mg. per cent; serum phosphorus between 2.2 and 3.2 mg. per cent; serum amylase 114. Gastrointestinal series revealed marked antral and duodenal spasm. No ulceration was seen. Electrocardiograms demonstrated short QT time; intravenous pyelograms revealed bilateral calcifications of the renal papillae. X-rays of the bones showed only proliferative changes secondary to a laminectomy performed seven years previously. After a febrile episode, believed to represent an infection of the urinary tract which was successfully treated with chlortetracycline, the patient underwent neck exploration. A 12 gm. parathyroid adenoma was removed from the right lower pole area. During the immediate postoperative period he appeared to do quite well. Fluid intake and urine output were carefully watched and appeared satisfactory. On the second postoperative day, however, the patient complained of inability to void and abdominal pain. No urine was obtained on catheterization. The abdomen was firm to palpation and there was generalized tenderness. The white cell count, which had been 5,000/mm.^{3} before the neck exploration, rose to 20,500 with 81 per cent polymorphonuclears and 12 per cent stab forms. The serum non-protein nitrogen rose to 110 mg. per cent. Flat plate of the abdomen was unremarkable. During the course of the day severe generalized abdominal pain continued. Wangensteen drainage afforded no relief The abdomen became more board-like. Two hundred cc. of urine was obtained on subsequent catheterization. Urinalysis was unremarkable. Finally, because of signs of an acute condition of the abdomen developing, the patient underwent laparotomy; the preoperative diagnosis was suspected perforated ulcer. Free, amber-colored fluid was present in the peritoneal space. The omental fat was necrotic. The pancreas was diffusely thickened, of very firm consistency, and estimated to be three times normal size. The duodenum, stomach and remainder of the bowel were unremarkable. No evidence of perforation at any site was noted. Some of the serum that had been drawn preoperatively for typing and cross-matching of blood was later found to have an amylase value of over 1,000 units. During the postoperative period the patient experienced episodes of disorientation and confusion. The serum calcium fell to a low of 7.0 mg. per cent and parenteral calcium gluconate was used although tetany never developed. He gradually became reoriented, returned to a normal diet and was mobilized. On the seventeenth postoperative day he was discharged much improved. Subsequently he returned to work and to date has felt well.

SUMMARY AND CONCLUSIONS

1. The cases of parathyroid adenoma at Duke Hospital for the past twenty years are reviewed. Ten of the total number of twenty-seven patients were seen in the past year.
2. The variations and modifications of the classic clinical pattern that require appreciation of the wide scope of this disorder are emphasized and representative cases are cited.
3. These and other considerations would seem to indicate a change in emphasis in the chemical criteria for establishing the diagnosis of hyperparathyroidism. The experimental evidence to support the concept of "phosphaturic" and "hypercalcemic" adenomas is mentioned.
4. Acute pancreatitis may be a postoperative complication of special interest in persons with parathyroid adenomas.

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ADDENDUM

Since July, 1955, six additional cases of hyperparathyroidism have been diagnosed at Duke Hospital and on the Medical Service of the Durham Veterans Administration Hospital, and adenomas were successfully removed in each

instance. At this writing, this makes an average of almost one case per month. Such a frequency is much higher than was previously appreciated and should encourage critical appraisal by all physicians of problems intimating this disorder.

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Seminar on Diseases of the Pancreas

Chronic Pancreatitis*

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CHRONIC pancreatitis progressively destroys the pancreas. This concept of progressive destruction is important to an understanding of the variability in the clinical picture, facilitating recognition of the disease and permitting a more rational approach to therapy. The progressive destruction results from repeated episodes of pancreatic edema or necrosis. Each episode subsides, leaving in its wake damage of varying degree in the pancreas. The pathologic consequences of the repeated acute episodes are extensive fibrosis, disappearance of acinar and islet cell tissue, pseudocyst formation, pancreatic calcifications and histologically demonstrable residues of non-lethal necrosis. From the functional standpoint, destruction of acinar and islet cells results in external pancreatic insufficiency and diabetes mellitus. During the early stages of chronic pancreatitis the reserve capacity of the pancreas is such that functional disturbances are only transiently demonstrable during the acute seizures. However, in the later stages destruction of tissue is sufficient to produce permanent alteration of function.

The fund of knowledge about chronic pancreatitis has gradually grown in the past two decades. The clinical syndrome of chronic pancreatitis in its more typical form has become well known and variations from the usual pattern are being recognized more frequently. The etiologic roles of alcohol, disease of the biliary tract, hyperlipemia and heredity have received consideration. The pathologic physiology has been well delineated. Laboratory procedures designed to aid in the recognition of external and internal pancreatic insufficiency in the intervals between seizures, as well as during the acute exacerbations of the disease, have been devised and appraised. In recent years the diagnosis of chronic pancreatitis has become relatively common, as familiarity with the syndrome has increased. Although the diagnosis and therapy of the disease are still not entirely satisfactory, these problems continue to receive serious consideration from surgeon and internist alike.

In this review of chronic pancreatitis we shall attempt to cover the salient features of the disease as it is seen in the early and late stages. Typical case histories are presented to illustrate problems in diagnosis and therapy.

ETIOLOGY

Comparatively little is known about either the predisposing or the precipitating factors in the etiology of chronic pancreatitis. Four factors which may be relevant deserve brief comment: alcohol, disease of the biliary tract, hyperlipemia and heredity.

Alcohol and Chronic Relapsing Pancreatitis. It has long been recognized that a relationship exists between alcohol and pancreatitis. In 1878 Friedreich alluded to "drunkards' pancreas."[1] The incidence of pancreatitis in alcoholics,[2,3] and of alcoholism in patients with pancreatitis,[4–8] is high. Chronic relapsing pancreatitis precipitated by alcohol is indistinguishable from that due to other causes. The observations of Carter[9] and of Domzalski and Wedge,[10] that elevated values for amylase in the serum were encountered frequently in alcoholics admitted to city hospitals, support the belief that alcohol has a definite effect on the pancreas, producing repeated mild, or subclinical, attacks of acute pancreatitis even in the absence of the more definite, clinically important, acute episodes. There is doubt about the mode of action of alcohol but it seems reasonable to accept the thesis that alcohol taken orally stimulates the secretion of hydrochloric acid by the gastric mucosa, which in turn stimulates formation of secretin. This results in vigorous pancreatic secretion, thus producing increased pancreatic

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intraductal pressure and rupture of the ducts or acini or both when there is obstruction to the outflow of pancreatic juice. The obstruction conceivably may be due to spasm, inflammatory narrowing, metaplasia, stones and the like. Contact of tenth-normal hydrochloric acid with the papilla of Vater has been shown to produce spasm of the sphincter of Oddi.[11] After large quantities of alcohol during an alcoholic debauch, edema of the mucosa of the duodenum and of the papilla of Vater may well produce some obstruction to the outflow of pancreatic juice and bile.

Disease of the Biliary Tract and Chronic Relapsing Pancreatitis. Although the incidence of disease of the biliary tract among cases of chronic pancreatitis is high, it cannot be assumed that the pancreatitis is necessarily the result of the associated disease of the biliary tract. Indeed, disease of the biliary tract may be secondary to pancreatitis, and conceivably the two conditions occurring simultaneously in the same person could be due to the same etiologic agent.[12] It is also possible that in some patients pancreatitis and disease of the biliary tract may coexist without any etiologic relationship to one another. Clinically one encounters patients with pancreatitis known to be free of primary disease of the biliary tract in whom the pancreatitis produces physiologic or organic obstruction of the common bile duct with secondary dilatation of the common duct, jaundice, cholangitis and even acute edematous cholecystitis. The edematous cholecystitis commonly disappears in the interval between painful seizures; a functioning gallbladder then is demonstrable by cholecystography or a normal gallbladder is found at necropsy, sequences which suggest that the disease of the biliary tract is secondary to the pancreatitis.

A comparison of cases of chronic pancreatitis and associated cholecystic disease with cases of chronic relapsing pancreatitis not associated with disease of the biliary tract reveals many similarities and remarkably few dissimilarities with regard to the clinical and pathologic features.[12] Chronic relapsing pancreatitis, regardless of the presence or absence of disease of the biliary tract, involves men more frequently than women, which is in contrast to the sex incidence in cholecystic disease. Frequently, in the established case of chronic relapsing pancreatitis with recurrent painful seizures, removal of the disease of the biliary tract does not alter the course of the pancreatitis. However surgical procedures, such as external and internal biliary drainage, have the same palliative effect in a substantial proportion of the cases of pancreatitis with and without disease of the biliary tract. The similarities in the clinical picture, pathologic physiology, course of the disease, pathologic alterations in the pancreas and response to therapy all point to the identity of chronic relapsing pancreatitis, regardless of the presence or absence of disease of the biliary tract.

The similarity of the clinical syndromes of disease of the biliary tract and of chronic pancreatitis renders the differential diagnosis difficult. Recurrent attacks of abdominal pain in the right upper quadrant that is referred through to the back are most frequently diagnosed cholecystic disease, since the latter occurs many times more frequently than does pancreatitis. Pancreatitis or some complication of disease of the biliary tract, such as empyema or rupture of the gallbladder, should be suspected when the pain lasts for days rather than hours. Pancreatitis should be strongly suspected when pain located primarily in the right upper abdominal quadrant is referred to the left upper quadrant, left anterior part of the thorax, left side of the back, or left shoulder, or when the pain starts in the left upper quadrant of the abdomen. When the patient has experienced previous attacks of characteristically severe and prolonged pain, pancreatitis should be suspected, either as the primary disease or secondary to disease of the biliary tract. Rarely does disease of the biliary tract, acute cholecystitis, empyema of the gallbladder or stone in the common duct without pancreatitis produce repeated, prolonged, severe seizures. The diagnosis of pancreatitis is more certain under these circumstances if values for serum amylase and serum lipase are elevated, or if steatorrhea, diabetes or calcification is present.

Hyperlipemia and Chronic Relapsing Pancreatitis. Chronic relapsing pancreatitis and hyperlipemia have been reported to coexist in perhaps eighteen cases.[13,14] Hyperlipemia may lead to a milky appearance of the serum or plasma and seems to be due primarily to a marked increase in neutral fats, sometimes with a less marked rise in the concentrations of cholesterol and phospholipids. Occasionally hyperlipemia is accompanied by xanthomatosis of the eruptive type, and by lipemia retinalis.[13,15] In a few of these cases hyperlipemia has been of the essential familial type. It is not known whether the pancreatitis, which is of the chronic relapsing type,

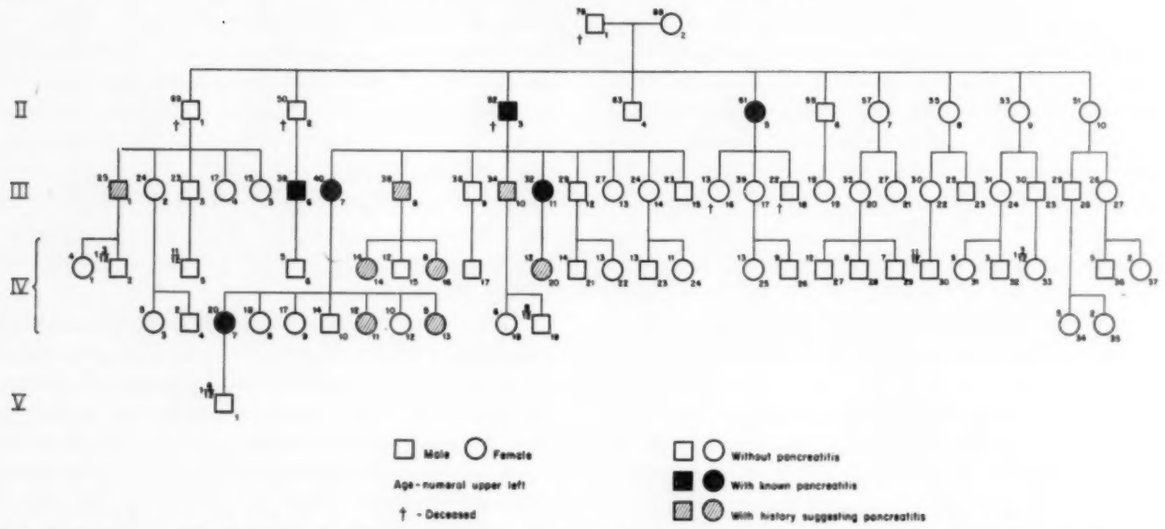

FIG. 1. Pedigree of K. family, in which hereditary pancreatitis is prevalent. Since preparation of this diagram IV-13, five years of age, has been found to have definite chronic relapsing pancreatitis.

is the result or cause of the hyperlipemia, or whether the association is coincidental.[13,15–20]

In the few reported cases of pancreatitis associated with hyperlipemia the onset has been either in early childhood or early adult life, thus resembling the hereditary form of chronic relapsing pancreatitis and differing from the more common, sporadically occurring variety. We have encountered three cases of chronic relapsing pancreatitis associated with hyperlipemia in young adults. In two of these cases the sequelae have not developed; the third patient has diabetes mellitus, possibly not a sequel to the pancreatitis inasmuch as an uncle is said to have had diabetes also. Wijnhausen's[17] patient had diabetes mellitus and creatorrhea; Adlersberg and associates[14] have reported on one patient with chronic relapsing pancreatitis and associated hyperlipemia in whom a pancreatic pseudocyst developed and on another patient who had mild diabetes. These would appear to be the only previously recorded instances in which patients with coexisting hyperlipemia and proved chronic relapsing pancreatitis have been seen at the stage in which sequelae of the pancreatitis had occurred. In the one case that has to our knowledge come to necropsy, the pancreatic acinar and islet cell tissue appeared essentially normal on microscopic examination; the interstitial tissue was the seat of fat infiltration and contained a number of lipide-filled macrophages.[21]

Our three cases fail to elucidate the relationship between hyperlipemia and pancreatitis. The apparent rarity of the association favors the view that the occurrence of the two diseases in the same person is coincidental. It is also possible that the same metabolic or physiologic process is responsible for the two conditions.

Hereditary Pancreatitis. It is not generally known that chronic relapsing pancreatitis may occur in a hereditary form. In 1952 Comfort and Steinberg[22] reported the extraordinary occurrence of chronic relapsing pancreatitis definitely affecting four members of a single family, with two other members probably affected. Since that time we[23] have recorded the pedigrees of two other such families. In one of these a young man and two of his maternal uncles definitely have chronic relapsing pancreatitis with sequelae; two other relatives are suspected of having pancreatitis. In the third family, seven persons are definitely affected, with at least seven others suspected of having, but not yet proved to have, the disease. The pedigree of the third family is detailed in Figure 1. We are unaware of other reports in which chronic relapsing pancreatitis has been discovered definitely to involve more than one member of a family, although there are two reports of pancreatitis associated with hyperlipemia in a child, with possible involvement of a single sibling.[16,20] We have recently encountered, but not yet studied, several other families in which the disease has affected two or more members.

The hereditary form of chronic relapsing

pancreatitis appears to be transmitted as a mendelian autosomal dominant gene. Although hereditary chronic pancreatitis clinically and pathologically resembles in most ways the sporadically occurring type, there appear to be several differences. The disease in the hereditary form would appear to begin in early childhood most often, whereas in the sporadic form symptoms usually begin in the third or fourth decade of life. A second difference has to do with sex incidence. So far, in the hereditary form of the disease, women have been involved half again as frequently as men, whereas in the sporadic form men usually have predominated[5,24] (sex ratio as high as six males to one female); with respect to sex incidence, therefore, the hereditary form of pancreatitis more closely resembles cholecystic disease.* A third difference between the hereditary and the non-hereditary forms of chronic pancreatitis is the relative infrequency of alcoholism among those with the hereditary form. It also has been true that gallstones have been uniformly lacking in the hereditary form. It would seem that these persons with hereditary pancreatitis must inherit some abnormality, perhaps of a metabolic nature, which predisposes them to the development of recurring attacks of pancreatitis which appear rather early in life. Hyperlipemia appears not to be a factor in the persons we have observed.

Hereditary pancreatitis will doubtless be recognized and reported with increasing frequency as physicians become increasingly aware of the entity. The hereditary form of the disease should be strongly suspected when chronic relapsing pancreatitis is encountered in a child or young adult, or when the attacks date back to childhood, especially when unattended by disease of the gallbladder and bile ducts. In our experience a careful inquiry under these circumstances not infrequently results in the discovery of pancreatitis in others in the family.

PATHOLOGIC ANATOMY

Gross Appearance. Chronic pancreatitis may involve the entire gland or may be localized in some part of it. During an acute exacerbation the examination may reveal diffuse edema, areas of necrosis and abscesses in the enlarged gland, as well as peripancreatic inflammation or necrosis. After the acute inflammation has subsided, the pancreas may be firm or hard and it may be nodular. Localized areas may be hard enough to simulate carcinoma. Infiltration with fat occurs and pseudocysts of variable size may be present. The pseudocystic contents may vary from cloudy, colorless fluid, to yellowish green, semisolid necrotic material and old or fresh blood may be present. Chemical analysis of the contents of the pseudocyst shows varying concentrations of pancreatic enzymes. The pancreatic ducts may be enlarged and may contain stones of calcium carbonate. In the final stages of chronic pancreatitis the gland may be small, hard and calcareous.

Histologic Examination. There is considerable variation in the microscopic picture also. Fibrosis is a rather constant finding and usually more interlobular than intralobular or interacinar in location. The pancreas in some sections is entirely replaced by fibrous connective tissue and there are frequently rather widespread atrophy and disorganization of the pancreatic acini and islets of Langerhans. There is usually infiltration with lymphocytes, plasma cells and sometimes eosinophilic leukocytes. Occasionally, acute suppuration is observed. Perhaps the most distinctive histologic feature, however, is the small, healed area of necrosis composed of giant cells and fibroblasts arranged about cholesterol-crystal clefts. (Fig. 2*c*.) Hemosiderin and calcium may both be deposited in the interstitial connective tissue. There is histologic evidence of dilatation of the smaller pancreatic ducts. These may contain laminated material, probably inspissated mucus, and concretions of calcium carbonate. Squamous metaplasia or squamatization of the ductal epithelium is sometimes observed. Interpreted in the light of the known clinical course of the disease, interstitial fibrosis and the residues of previous necrosis appear to be the regressive, end stage of repeated attacks of acute inflammation. It is also possible that a continuing chronic inflammatory process may produce these changes, especially in those cases in which clinical evidences of acute exacerbations do not appear. The acute inflammation may be of the interstitial type, as described by Archibald,[25] Elman[26] and others,[27,28] but in those cases in which residual necrosis is observed the inflammatory process appears to have been in the nature of repeated sublethal attacks of acute hemorrhagic pancreatitis. Either type may be followed by fibrosis and atrophy. The

* It should be noted that the more frequent occurrence of hereditary pancreatitis in women may only reflect chance variation in a small population sample.

pseudocysts are interpreted as being the result of acute inflammation, necrosis and subsequent digestive action of the liberated pancreatic enzymes.

Changes in Adjoining Organs. The neighboring structures may be affected by pressure of the enlarged pancreas or by involvement by the disease. Thus the duodenum may be partially obstructed or duodenitis may be produced, with resultant gastric retention and retention type of vomiting, and sometimes upper gastrointestinal hemorrhage. The common bile duct may be similarly obstructed, producing jaundice, ascending cholangitis and occasionally acute edematous cholecystitis. Ileus of a localized or generalized character or hypermotility of the bowel may be observed. Thrombosis of the nearby splenic vein may produce splenomegaly, and friability of the mesenteric veins involved by the inflammatory process may constitute a real surgical hazard during performance of operations on the pancreas. We have encountered a few cases in which associated thrombosis in the superior mesenteric or splenic vein had resulted in gastric and esophageal varices, with consequent repeated variceal hemorrhage. Pleural effusions, at times hemorrhagic, may follow acute exacerbations. Eventually the degenerative complications of diabetes mellitus may also be observed.

PATHOGENESIS

It is generally accepted that the destructive process of pancreatitis is the result of the passage of activated enzymes from the ducts into the pancreatic parenchyma, the lipase and trypsin liberated producing the digestion of fat and protein in and around the gland, as well as the edema and necrosis.[29] There is some disagreement, however, in regard to the mechanism by which such extravasation of enzymes occurs. Only the four principal pathogenetic theories will be mentioned.

The obstructive theory holds that rupture of the pancreatic ducts is the result of increased intraductal pressure caused by a combination of increased secretory activity of the pancreas and obstruction of the pancreatic duct. Experimentally, acute pancreatitis has been produced by rupture of pancreatic ducts as the result of rapid injection, under rather high pressures, of bile, India ink and colored Locke's solution.[30–32] Acute pancreatitis has also been produced by simultaneous obstruction of the pancreatic duct (by ligation or by spasm induced by opiates) and stimulation of secretion by administration of secretin[33–35] or methacholine (mecholyl)® chloride,[36] or by the ingestion of food.[35,36] Clinically, acute pancreatitis is observed when the pancreatic duct is obstructed by stone in the common bile duct,[37,38] or by cancer of the ampulla of Vater.[37] The clinical picture of acute pancreatitis has followed ingestion of an overdose of morphine also.[39] Presumably, acute pancreatitis is also seen clinically when edema of the mucosa of the papilla or spasm of the sphincter of Oddi is induced by an excessive intake of alcohol, or by disease of the biliary tract when accompanied by stimulation of pancreatic secretion by alcohol or by large meals.[4,9,31,35,36,40–42] The role of obstruction and hypersecretion in combination in provoking pancreatitis appears to be well supported.

The common channel theory, first advocated by Opie,[43,44] and emphasized by Archibald,[45] postulates that pancreatic destruction results from reflux of bile into the pancreatic duct, with activation of pancreatic enzymes, in the presence of a common channel between the common bile duct and the pancreatic duct when the ampulla of Vater is blocked by calculus or by spasm or edema of the sphincter. That a common channel frequently exists seems to have been established by anatomic dissections[30,46,47] as well as by cholangiographic observations[48–50] and those made at operative procedures on the sphincter of Oddi.[48] Similarly, the flow of radiopaque material into the pancreatic duct from the common bile duct and duodenum in normal persons and during operative and postoperative cholangiographic procedures in patients with disease of the biliary tract and pancreas fully justifies the belief that bile likewise enters the pancreatic duct.[49,50] However, the frequency with which radiopaque material enters the pancreatic duct and, consequently, the presumed frequency with which bile enters this duct without producing pancreatitis seemingly minimizes the factor of activation of the pancreatic juice by bile as a cause of pancreatitis. In fact, there is reason to believe, as pointed out by Hicken and McAllister,[49] that entrance of bile into the pancreatic duct may be a normal, or physiologic, occurrence. The observation of Cross and coworkers[51] that, in the dog at least, bile may flow through the pancreatic duct at physiologic pressures without producing pancreatitis like-

wise tends to discount the importance of bile in the pancreas. Such considerations have shifted emphasis in the common channel theory away from the activating effect of bile to the role of obstruction at the ampulla, converting the common bile duct and pancreatic duct into a closed system in which perhaps secretion of bile and pancreatic juice builds up pressures to a degree sufficient to cause pancreatitis. It is conceivable that several factors may contribute. In the presence of a common channel, internal and external drainage of the common bile duct or sphincterotomy becomes a reasonable procedure by virtue of relief of intraductal pressure, permitting drainage and subsidence of inflammation.[48,52–54]

The toxic theory should be mentioned, although chronic pancreatitis of the toxic type does not often become a clinical problem. It has been suggested that alcohol may produce chronic pancreatitis by its direct toxic effect upon the organ, as well as by its effect on the acid-secretin mechanism.[42] Chronic pancreatitis without clinical, acute pancreatitis occurs not only in alcoholism[9,10,29] but also in association with other diseases, such as ileitis and ulcerative colitis. Experimentally, pancreatitis has been produced by administration of ethionine, the ethyl analogue antagonist of the essential amino acid, methionine.[55–59] Administration of ethionine has been shown to interfere with the uptake of radioactive methionine by body tissues of rats and mice.[57,60,61] By interference with protein metabolism in some way ethionine causes degeneration of the acinar cells of the pancreas, with subsequent pancreatic atrophy. A clinical counterpart of the action of ethionine has not been noted, however.

The infectious theory would not seem to account for many cases of chronic pancreatitis. It is known that acute pancreatitis may complicate mumps,[62,63] scarlet fever[64] and dysentery.[65] Apparently the lymphatics from the gallbladder do not enter the parenchyma of the pancreas,[66] so that the possibility of bacterial infection occurring by this route has now been largely discarded. Cultures of material obtained from acutely diseased pancreatic glands have rarely produced any growth of organisms until secondary infection has occurred.[29] The possibility that an infectious agent may be responsible for pancreatitis, even the chronic variety, has not been fully explored in so far as most of the viruses are concerned.[67]

PATHOLOGIC PHYSIOLOGY

Dysfunction of Acinar Cells. During the acute seizures dysfunction of acinar cells may be temporarily produced and is evidenced by increased values for serum amylase and lipase, and sometimes by transient steatorrheal diarrhea. The values for serum enzymes reach maximal levels rather early, rapidly returning to normal after the attack ceases. Continuous elevations may be observed when the attacks, though mild, occur in rapid succession or when pancreatitis is active for long periods. Concentrations of serum amylase and lipase are not always increased simultaneously. It is presumed that these elevations result from obstruction of the pancreatic ducts, with rupture of the ducts or acini and entrance of the pancreatic juice into the lymphatics. It is also possible that hypersecretion may play a role.

As pancreatic destruction progresses, permanent functional disturbance of the acinar cells occurs. At this point the remaining functioning acinar cells may be insufficient to produce elevated values for serum amylase and lipase during an exacerbation. Acinar dysfunction is also evident in faulty digestion and absorption of fats and proteins, with consequent loss of large amounts of fat and nitrogen in the feces—evidences of extensive parenchymal damage. The stools typically become bulky and fatty-appearing, and sometimes liquid fat is to be observed floating on the water of the toilet. The bulkiness of the stools may contribute to the frequency of bowel movements.

Disturbance of Function of Islet Cells. Early in the course of chronic pancreatitis temporary disturbance of islet cell function may occur, perhaps less frequently than transitory disturbances of secretion of the acinar cells, and is indicated by transitory glycosuria and hyperglycemia or a positive result with the glucose tolerance test. In advanced chronic pancreatitis destruction of islet cell tissue has commonly progressed to the point that frank diabetes mellitus is encountered.

CLINICAL MANIFESTATIONS AND COURSE OF THE DISEASE

Chronic pancreatitis begins most often in the third or fourth decade of life but may begin in childhood or old age. It occurs much more frequently among men than among women and, unlike cholecystitis, does not have a predilection for obese persons.

The clinical syndrome is readily divided into two stages. In the earlier stage—that is, before the development of the sequelae of diabetes, steatorrhea, calcifications and pseudocyst formation—the outstanding clinical feature is the painful seizure. In the later stage, to the painful seizures are added the sequelae of the disease. From the standpoint of diagnosis and therapy, it is helpful to consider the two stages separately.

THE EARLY STAGE OF THE DISEASE

The following is an illustrative case in which the disease was well established, but diabetes mellitus, steatorrhea and calcifications were not present.

CASE 1.* A white man, aged thirty-nine years, first came to the Mayo Clinic on September 4, 1934. He had used alcohol heavily. In August, he had experienced his third attack of high epigastric pain, two similar attacks having occurred in the preceding six months. After a few days of relatively mild pain high in the epigastrium, he became acutely ill, the pain being very severe and spreading through to the back and to the anterior portion of the thorax. Breathing aggravated the pain; nausea, vomiting and abdominal distention accompanied it. There was evidence of mild shock. The systolic blood pressure dropped to 84 mm. Hg. His maximal temperature was 101.5°F. The leukocyte count reached 19,000 per cu. mm. of blood.

During the examination seventeen days after he had become acutely ill, mild jaundice, epigastric tenderness and rigidity of the muscles in the upper part of the abdomen were noted. The concentration of bilirubin was 1.2 mg. per 100 ml. of serum, and the van den Bergh reaction was direct. The erythrocyte sedimentation rate was slightly elevated.

The general condition of the patient improved. Roentgenograms of the gallbladder and stomach failed to show significant disease. The clinical diagnosis was acute pancreatitis.

Severe, painful episodes similar to the above recurred at intervals of about one year. Repeated roentgenologic examinations of the gallbladder showed that this organ functioned normally, without visible stones, and physical examination and laboratory investigations between the acute seizures always gave normal results. Following a severe attack associated with jaundice in February, 1939, abdominal exploration revealed diffuse hardening of the pancreas, more so in its head than in the other portions; the gallbladder was thick-walled and edematous and did not contain stones, and there was moderate dilatation of the common bile duct, which also did not contain stones. Probes were passed through the ampulla with difficulty. Cholecystostomy was done and a T tube was placed in the common bile duct. This came out spontaneously six weeks after operation.

Attacks occurring in August, 1940, December, 1942, and April, 1943, were severe, lasting four to ten days and being characterized by nausea, vomiting, constipation, fever and leukocytosis. Values for serum amylase, lipase and bilirubin during the attacks were repeatedly normal. The last attack occurred in 1944, shortly before his last admission. At this time, disturbances of pancreatic and cholecystic function were not demonstrated. Left pneumonectomy was carried out for carcinoma of the lung, following which procedure the patient died, in July, 1944.

At necropsy the gallbladder was normal. The consistency of the pancreas was greatly increased; the gland weighed approximately 70 gm. Marked fibrosis was visible on examination of the cut surface of the gland (Fig. 2*a*) and there were several small pseudocystic areas which contained pale, yellowish green or dark semi-solid material. Histologic study revealed typical features of chronic pancreatitis, including areas in which fibroblasts and giant cells were arranged about cholesterol-crystal clefts (Figs. 2*b* and *c*).

Comment. In this case the repeated attacks were characteristically severe and of several days' duration. Although clinically the usual sequelae of chronic pancreatitis had not developed, destruction of the pancreas was clearly visible on pathologic examination, with fibrosis, atrophy and necrotic residues.

The recurring painful seizures may be preceded by nondescript dyspepsia but with the advent of the first acute painful attack there is rarely any doubt that organic disease has made its appearance. The painful seizure is usually gradual in onset and tends to be constant, although waves of increased intensity may be superimposed. Although the pain may be mild and may vary in intensity from one attack to another, it is characteristically very severe and frequently requires repeated injections of opiates for relief. Opiates may not terminate the attack as they so often do in cases of uncomplicated biliary colic. During a seizure the patient commonly assumes the so-called pancreatic position, with trunk flexed forward and pressure exerted against the abdomen. He tends to be most uncomfortable lying supine. Although seizures may last for only a few hours, they are most characteristic when they last for longer periods. Most commonly the attacks last for one or two days but sometimes they persist for two to six days or for as long as four weeks. The pain is usually epigastric in location but may involve

* Case reported previously.[5]

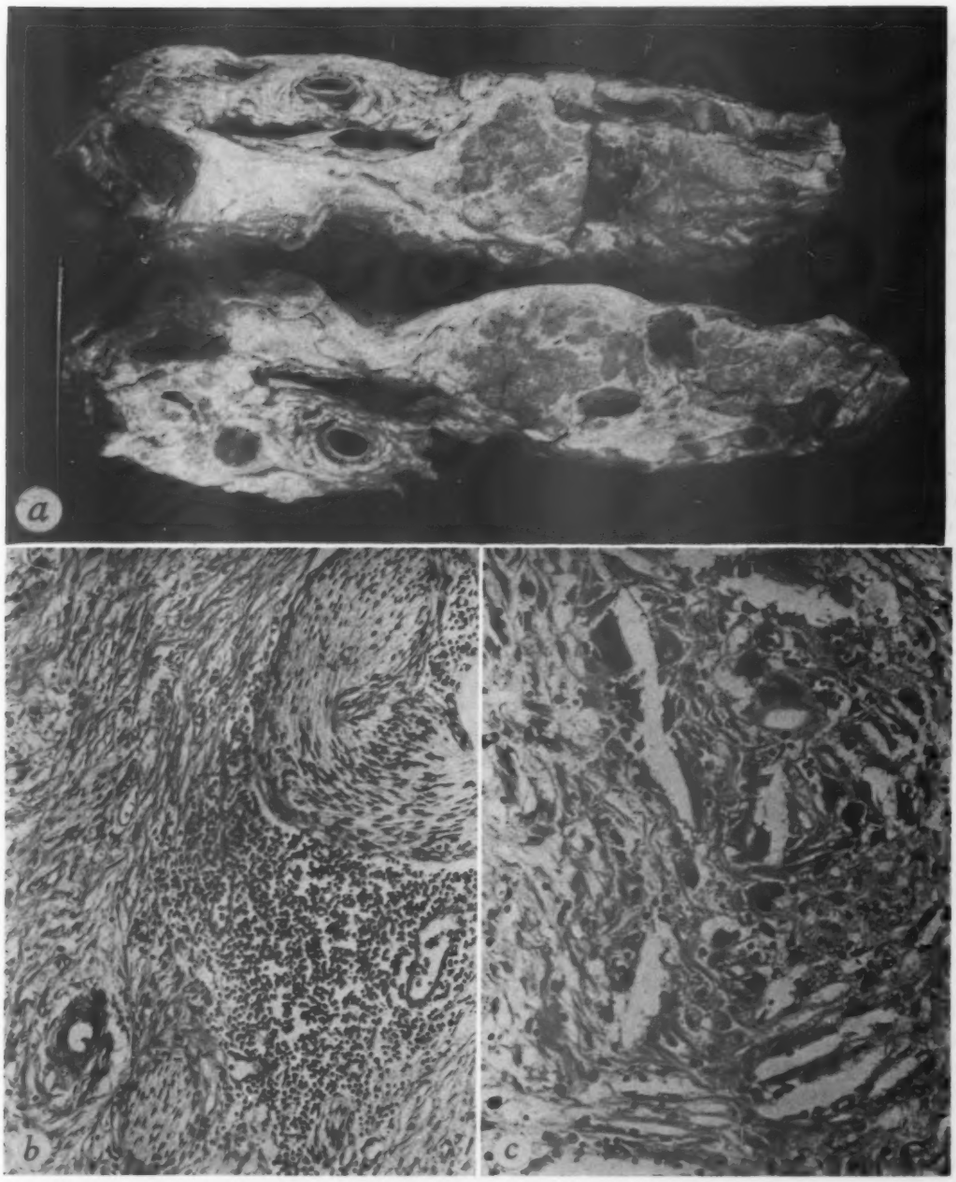

FIG. 2. Case I. Pancreas. (*a*), Extensive fibrosis, areas of necrosis and pseudocyst formation are evident. (*b*), Fibrosis and perineural distribution of lymphocytes are shown; hematoxylin and eosin, original magnification × 125. (*c*), Fibroblasts and giant cells are arranged about cholesterol-crystal clefts; hematoxylin and eosin, original magnification × 200. (Reprinted with permission from: COMFORT, M. W., GAMBILL, E. E. and BAGGENSTOSS, A. H.[6] Chronic relapsing pancreatitis: study of twenty-nine cases without associated disease of biliary or gastrointestinal tract. *Gastroenterology*, 6: 239–285, 1946.)

any part of the abdomen. Not infrequently it is located in the right subcostal region or may spread there from the epigastrium and is referred to the right side of the back. Pancreatitis should be suspected strongly when the epigastric pain and associated tenderness are referred to the left upper part of the abdomen and through to the left side of the back, or when the pain begins in the left upper part of the abdomen.

The acute painful exacerbation is sometimes accompanied by jaundice, chills, fever and sweating. A peculiar cyanosis has been noted. Abdominal distention may be conspicuous, raising the question of intestinal obstruction.

Enlargement of the spleen or liver may occur and occasionally the enlarged pancreas may be palpable as a tender mass lying transversely across the epigastrium. Tenderness is usually present in the region of maximal pain and frequently persists for twenty-four hours or longer after the pain has disappeared. Muscle guarding is common, although boardlike rigidity suggestive of perforation of a viscus is rarely observed. Shock may appear, in association with extensive pancreatic necrosis. Cullen's[68] sign and Turner's[69,70] sign occasionally are observable.

Between attacks the patient may be entirely asymptomatic, although not infrequently he experiences postprandial fullness or ulcerlike dyspepsia. The attacks occur at varying intervals. Sometimes remissions last for years, although quite commonly attacks recur once or twice annually and, as the disease progresses, the frequency of the seizures commonly increases, attacks occurring as often as once or twice a month. Most commonly the attacks continue for five or more years before the diagnosis is established.

Urinalysis may show the results of renal irritation: albuminuria, cylindruria and microscopic hematuria. Glycosuria may occur transiently. Mild anemia, usually hypochromic, is not infrequent and leukocytosis often occurs during the exacerbation. Eosinophilia has been observed in a few cases;[5,71] one of our recent patients exhibited 27 per cent eosinophilia. Herfort[72] has reported the occurrence of lymphopenia within forty-eight hours of the onset of attacks of pancreatitis. The erythrocyte sedimentation rate is frequently increased. The fasting concentration of blood sugar may be increased transiently and the glucose tolerance test sometimes discloses diminution of reserve of islet cell function during an acute exacerbation. The concentration of bilirubin in the serum is commonly slightly elevated during the painful seizures and may remain abnormal after the pain has disappeared.

The elevation of values for serum amylase and lipase characteristic of the acute seizures have been discussed. Both of the substances should be determined inasmuch as the concentration of either of them may be increased in the presence of a normal concentration of the other. Because elevated values may be seen in cases of perforated gastroduodenal ulcer,[73] peritonitis,[74] intestinal obstruction,[75] bronchogenic carcinoma[76] and other diseases such as mumps,[62,63] they should be subjected to critical appraisal before being interpreted as evidence of pancreatic acinar dysfunction. Renal insufficiency[77] has also been cited as a cause for elevated values for serum amylase and lipase, although in our own experience these values have usually been normal in patients with this condition.[78] It is now well established that opiates may result in rather striking elevations of values for serum enzymes. Contrary to common belief, the heights to which concentrations of serum amylase and lipase may attain following administration of opiates are frequently as great as those seen in acute or chronic pancreatitis.[79-83] Values for serum calcium may fall below normal, usually only slightly, but sometimes as low as 6 or 7 mg. per 100 ml. of serum. The greatest decreases in concentration occur in the most severe cases, usually in cases of hemorrhagic necrosis, and generally connote a poor prognosis.[76] The prothrombin time may be elevated when jaundice is present. Hypoproteinemia occasionally is seen during prolonged, severe attacks. Innerfield and coworkers[84] have reported elevations of blood antithrombin titer during acute exacerbations of chronic relapsing pancreatitis but Dreiling[85,86] and others[87,88] have not found this test to be of real diagnostic help. Zollinger and associates[89] and others[74,75] have stressed the value of amylase and lipase determinations on peritoneal fluid obtained by diagnostic paracentesis, and occasionally demonstration of high concentration of these enzymes in pleural fluid also provides diagnostic help. During this early stage in the course of chronic pancreatitis examination of the feces usually fails to reveal steatorrhea and azotorrhea.

Rather often after the patient has experienced several attacks of pancreatitis, and sometimes after only one severe episode when sufficient pancreatic destruction has occurred, subclinical grades of pancreatic insufficiency are demonstrable. The glucose tolerance curve not infrequently is of the diabetic type, disclosing latent diabetes mellitus.[24] Examination of the duodenal contents before and after administration of various stimulants of external pancreatic secretion is now a well established diagnostic procedure. Although neostigmine (prostigmin®) bromide, bethanechol (urecholine®) chloride and methacholine (mecholyl®) chloride have all been employed as test substances, secretin has been used more frequently for this purpose. There is agreement that the volume and bicarbonate

responses are the most significant following administration of secretin. This observation is in accord with the physiologic facts, since secretin is known to evoke a copious flow of thin, watery pancreatic secretion of high bicarbonate but low enzyme content, the latter presumably representing the washing out of enzymes preformed in the pancreatic acini. Unquestionably, the secretin test carefully conducted will provide evidence of disturbance of external pancreatic function in a considerable proportion of cases before the sequelae of calcifications, diabetes and steatorrhea have appeared.[90,91] However, the secretin and allied tests are somewhat difficult to perform and are time-consuming; performance of these tests requires a rather high degree of technical skill. In addition, in our experience equivocal results are not infrequent early in the course of pancreatitis when clear-cut demonstration of external pancreatic insufficiency would be particularly helpful in confirming the diagnosis.

Chemical analysis of all feces passed during a three- to six-day period, while the patient is ingesting a standard test diet which provides approximately 100 gm. of fat and 19 gm. of nitrogen daily,[92] occasionally discloses abnormal amounts of fat and nitrogen in the feces in the absence of clinical evidence of external pancreatic insufficiency in cases in which advanced destruction of the organ, as indicated by gross steatorrhea or the other sequelae, is not present. On a diet that contains 100 gm. of fat, normal persons have been found to excrete less than 7.0 gm. of fat and 2.5 gm. of nitrogen daily.[92] Recently the fasting level of plasma carotene has been reported to correlate well with fecal fat excretion.[93] This colorimetric test is simply and quickly performed but whether it will prove adequate to replace quantitative fecal analysis remains to be seen. Others have recently reported detection of steatorrhea by determination of the radioactivity of stool collections and blood samples following administration of I-131 tagged glycerol trioleate in peanut oil;[94] other tests are being assayed, including the I-131 labeled protein meal,[95] the paritol-C test[74] and study of the rate of phospholipid synthesis.[96] None of these has as yet come into wide clinical use in the study of patients with pancreatitis.

Provocative serum enzyme tests have been studied in an effort to facilitate the establishment of the diagnosis of pancreatic lesions, including pancreatitis before the development of definite sequelae. These tests measure serially the values for serum amylase or serum lipase or both following stimulation of the pancreas by administration of secretin, mecholyl, urecholine or prostigmin, with or without morphine, and they have produced definite increases of enzymes in patients with pancreatitis.[33,97,98] However, similar increases may be produced in normal persons and may fail to occur frequently enough in patients with pancreatic disease to limit the usefulness of these tests, in our experience as in the experience of others.[86,99] Employing the secretin serum enzyme test in a series of sixty-four patients with various gastrointestinal disorders, Gross, Mathieson and Power[100] were unable to provoke any increases of serum amylase and observed increases of serum lipase in only four patients, none of whom had unquestioned chronic relapsing pancreatitis. Innerfield and associates[84] have reported elevations of antithrombin titer to be provoked during remissions in cases of chronic pancreatitis by the subcutaneous administration of prostigmin or urecholine. If pleural or peritoneal fluid has accumulated between seizures, demonstration of high amylase and lipase content of such fluid may be of assistance in establishing the correct diagnosis.

Cholecystographic examination may provide worthwhile information about the presence or absence of disease of the gallbladder. If performed during an acute seizure, evidence of a non-functioning gallbladder should be discounted and the cholecystographic examination repeated after recovery is complete. Roentgenograms of the pancreas are not revealing in this early stage of the disease. Roentgenologic examination of the stomach and small bowel may reveal various abnormalities, including duodenal obstruction, duodenal or gastric deformity or disturbances of gastrointestinal motility, as discussed previously. The duodenal deformity may be mistakenly attributed to chronic duodenal ulcer.

In these early cases, in which the acute painful seizure is often the sole clinical manifestation of chronic destruction of the pancreas, the diagnosis should be suspected when the pain is characteristically severe, recurs after each hypodermic injection of morphine and lasts for one or more days, especially when there is a history of similar attacks and when the pain has involved the left upper part of the abdomen and left side of the back. Elevated values for serum amylase and

lipase during the attacks lend diagnostic confirmation, provided other causes of elevated values are excluded, and a distinct decrease in the concentration of serum calcium is also of diagnostic help.

Conditions that commonly require exclusion are disease of the biliary tract, perforation of a viscus, intestinal obstruction and myocardial infarction. Disease of the biliary tract is considered elsewhere in this paper. Perforated peptic ulcer should be suspected when there is increasing generalized rigidity of the abdominal muscles. Increases of serum amylase and lipase following the perforation of an ulcer are usually slight to moderate and should not offer great confusion in differential diagnosis.[73,101] Intestinal obstruction can be closely simulated by pancreatitis. Since slightly elevated values for serum enzymes may occur in intestinal obstruction, only amylase values of more than 500 or 600 Somogyi units or lipase values of more than 1.5 ml. of tenth-normal sodium hydroxide are helpful in making this differential diagnosis.* When the pain is referred into the anterior part of the thorax and when shock occurs, the acute exacerbation of chronic pancreatitis may simulate myocardial infarction. It is helpful to remember that the pain of acute exacerbation of chronic pancreatitis is seldom referred to the neck or to the arms. In those cases in which painful seizures have recurred many times, myocardial infarction as an explanation for all the attacks is unlikely. Elevated values for serum amylase and lipase, decreased values for serum calcium, and the appearance of clinical jaundice are helpful differential points. Unfortunately, the value for serum transaminase apparently may be elevated in either condition.[103] The failure of the changes of myocardial infarction to appear in the electrocardiogram likewise is helpful. On the other hand, the occurrence in pancreatitis of electrocardiographic changes suggestive of or consistent with acute myocardial infarction may be confusing.[6,104–106] The basis for the electrocardiographic changes associated with pancreatitis is not known. From the clinical standpoint, if an electrocardiogram recorded during the course of an acute exacerbation of chronic pancreatitis leads to error, it will be in the direction of conservative management. Psychoneurotic patients with somatization manifest as abdominal pain and dyspepsia frequently represent difficult problems in the differential diagnosis. Although some features in the symptomatology of patients with these functional disorders may suggest chronic pancreatitis without sequelae, other features are apt to be bizarre. Rarely does the neurotic patient describe the full constellation of distinctive symptoms which usually characterize the painful seizures of chronic relapsing pancreatitis.

* Maclay modification of the Cherry and Crandall method for lipase.[102]

THE LATE STAGE OF THE DISEASE

Eventually, as destruction of the pancreas proceeds, diabetes mellitus, steatorrhea and deposits of calcium in the parenchyma of the gland or as stones in the duct system will appear in many cases. The diagnosis is simplified when these distinctive and diagnostic sequelae appear. The following case exemplifies the late stage of chronic pancreatitis, pancreatic calcifications and abscess, steatorrhea, and diabetes mellitus with peripheral neuritis having developed.

CASE II. A man, fifty-four years of age, had been under our care from time to time since 1947, when he came seeking relief from recurring bouts of upper abdominal pain. These pains had begun in 1945 and were severe; some lasted only a short time but others lasted several days. In May, 1948, mild diabetes mellitus was discovered. A paternal uncle was known to be diabetic. The patient had indulged heavily in alcohol, often having consumed as much as a fifth of a gallon of whisky daily in the previous ten years. Abdominal exploration disclosed in the head of the pancreas a mass 10 cm. in diameter, firmness of the body and tail of the pancreas, and a fairly large quantity of yellow, slightly turbid, thin peritoneal fluid, which was evacuated. A biopsy specimen of the mass in the head of the pancreas showed acute hemorrhagic inflammation (Fig. 3); the gallbladder and appendix were not diseased.

In August, 1948, an episode of severe, steady epigastric pain spreading to the right subcostal margin lasted for three days. Vomiting occurred repeatedly during this attack and on examination pronounced epigastric tenderness was noted. The value for serum amylase was 1,600 units; moderate amounts of insulin were required to control glycosuria. Bilateral splanchnic-nerve block resulted in complete relief of the abdominal pain, so that in September bilateral splanchnicectomy was performed. Following this procedure the patient felt well for three months; the diabetes continued to require moderate amounts of insulin for control.

Attacks of severe right upper, right lower and epigastric abdominal pain recurred in February, 1949. One such attack lasted for two weeks, during which the maximal temperature was 101°F. and a tender

mass could be felt in the epigastrium. Surgical exploration on September 30, 1949, revealed that the epigastric mass was a large abscess, which was incised and drained. At this time roentgenograms of the pancreas first revealed calcifications to the right of the second and third lumbar vertebrae in the region of the head of the pancreas. The pain did not recur after the abscess was drained.

In January, 1954, the patient began to have frequent, bulky, light-colored stools, some containing free oil in droplet form which floated on the surface of the water. The steatorrheal diarrhea was satisfactorily controlled thereafter by a relatively low intake of fat and the administration of triple-strength pancreatin tablets. However, in August, 1955, other complications appeared. Numbness and prickling sensations in the fingertips and toes, as well as aching throughout the legs, were noted. Slight diminution of sensation could be demonstrated objectively. Treatment with large doses of vitamin B complex and abstinence from alcohol were followed by disappearance of the signs and symptoms of peripheral neuritis. He followed a careful dietary regimen, maintained his weight and felt fairly comfortable. Control of the diabetes required 25 to 30 units of Lente insulin each morning. However, in December, 1955, satisfactory progress was interrupted by an episode of recurrent vomiting followed by melena. The patient was found to be in diabetic acidosis. Roentgenologic examination of the stomach revealed a deformity that was interpreted as the result of duodenal ulcer. Free gastric acidity was 26 clinical units one hour after an Ewald-type test meal. The total quantity of gastric contents recovered at the end of one hour was 325 ml., although the contents did not have a retention odor or contain food remnants. At no time had the patient experienced abdominal pain characteristic of duodenal ulcer but on a program of the ulcer type he had no further vomiting spells.

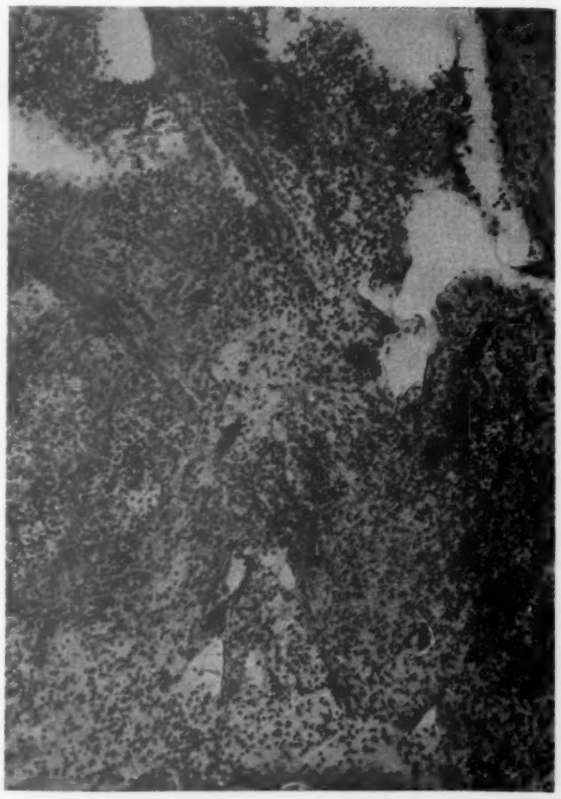

FIG. 3. Case II. Acute hemorrhagic pancreatitis visible in biopsy specimen; hematoxylin and eosin, × 70.

When recurring painful seizures of characteristic duration and severity occur together with pancreatic calcification, the diagnosis of chronic pancreatitis is not to be questioned. Calcareous deposits in the head of the pancreas are seen most frequently just to the right of the vertebral column at the level of the lower half of the first, and the upper half of the second, lumbar vertebrae. However, because the pancreas varies somewhat in its location, depending upon the patient's habitus, the calcifications are sometimes seen as high as the level of the eleventh thoracic vertebra and as low as the level of the third lumbar vertebra.[107,108] Although the calcification is most frequently seen in the head of the pancreas, it may be present in all parts of the organ. In some cases it is so extensive that the shape of the pancreas from head to tail is seen in the roentgenogram. The calcareous areas vary greatly in shape and size. In many instances they are tiny, being only a few millimeters in diameter, but sometimes larger, well circumscribed deposits are encountered, most commonly in the head and the body of the pancreas. In most instances a roentgenologic diagnosis of pancreatic calcifications can be made with relative ease because of location, size, shape and density of the calcareous deposits.

Pancreatic calcifications must be differentiated from calcified gallstones in the gallbladder and common bile duct, renal calculi, calcifications of the abdominal aorta and of the arteries of the celiac axis and calcified mesenteric lymph nodes. Gallstones are usually situated more laterally and are not often as densely calcified as are calcific deposits in the pancreas. Renal calculi lie lateral to the pancreatic region. Arterial calcifications are usually linear or ringlike and can easily be identified in the lateral view. Calcified mesenteric nodes in the region of the head of the pancreas most frequently present a diagnostic problem but as a rule the so-called

mulberry appearance of calcified nodes and their presence in other parts of the abdomen are identifying characteristics. Demonstration of calcification typical of that seen in chronic relapsing pancreatitis, with or without diabetes mellitus and steatorrhea, is in itself highly diagnostic. It even permits diagnosis of chronic pancreatitis in those rare cases in which abdominal pain is minimal or absent.

When, in the absence of pancreatic calcification, the characteristic seizures become complicated by subsequent development of diabetes mellitus, there is some question about the relationship of the two conditions because the diabetes may be unrelated to the painful seizures. However, when hyperglycemia and glycosuria first appear during the attack, especially when the familial history for diabetes is negative, the pancreatitic origin of the diabetes is more likely. The diabetes of pancreatitis varies greatly in severity from one case to another and there are apparently no special characteristics by which it may be distinguished from the ordinary variety. It is possible that the peripheral neuritis in Case II was alcoholic or nutritional in origin and not a complication of diabetes mellitus. In other cases of chronic pancreatitis with diabetes in which alcohol is not a possible etiologic factor peripheral neuritis and also ischemic ulceration of the lower extremities have been observed. In at least one other case of which we have knowledge the diabetes was complicated by intercapillary glomerulosclerosis.

Steatorrhea should be suspected whenever the description of the stools suggests an excessively large volume or content of fat, and the diagnosis should be pursued if microscopic examination of the feces discloses fat in excess. A pancreatitic origin for the steatorrhea should especially be suspected when attacks of abdominal pain characteristic of acute or subacute pancreatitis have recurred over the years. Persistent steatorrhea is a late development and indicates extensive destruction of the pancreas. As we have seen, concomitantly with the development of steatorrhea, pancreatic calcifications or diabetes or both frequently appear and serve to locate the pathologic process in the pancreas. When the fat content of the stool is high, gross inspection will disclose its fatty character. Usually in the presence of steatorrhea, fat globules will be found on microscopic examination of the feces and can be revealed more strikingly by staining the fecal smear with Sudan III. These are satisfactory screening procedures but they are not diagnostic and therefore should be confirmed by more precise quantitative procedures, preferably with the patient on a test diet, as described previously.

Steatorrhea often may be demonstrated by quantitative analysis of a single stool collected while the patient is taking an ordinary hospital diet if the fat (total lipide) comprises 30 per cent or more of the dry weight of the feces.[109] However, this type of test may give a falsely negative result since values of less than 30 per cent are sometimes obtained even in the presence of marked steatorrhea; this occurs when the quantity of the non-fatty constituents of the feces is also increased. Chemical measurement of the total quantity of fat and nitrogen in the feces over a period of three to six days with the patient ingesting one of the standard test diets[92] is a more dependable procedure.

In advanced chronic pancreatitis the secretin test characteristically demonstrates deficient external pancreatic secretion.[86,90,91] However, at this stage of the disease the test is rarely necessary to establish the diagnosis. Rather frequently in these advanced cases insufficient pancreatic acinar cells remain to produce elevated values for serum enzymes spontaneously during attacks, or upon stimulation with secretin or the other stimulants of external pancreatic secretion.

ATYPICAL CHRONIC PANCREATITIS IN THE LATE STAGE

Although the severe, prolonged, painful seizure is the hallmark of most cases of chronic pancreatitis, occasionally this distinctive feature is lacking. The pain may be short and mild, or it may even be absent. In the absence of pain the diagnosis is seldom suspected except in rare cases in which (1) palpation of the pancreas at surgical exploration for other causes reveals the disease, (2) a roentgenogram of the upper part of the abdomen by chance discloses calcification, or (3) steatorrheal diarrhea resulting from advanced destruction of the parenchyma of the organ takes the patient to the physician. These atypical cases, then, are characterized by any or all of the sequelae of chronic pancreatitis in the absence of clinically significant abdominal pain. Occasionally these cases present with painless jaundice of obstructive type. Although infrequently encountered, painless pancreatitis unquestionably occurs[24,110,111] and, because of certain unique aspects relating to

diagnosis and management, deserves special comment.

Painless chronic pancreatitis in which a chance roentgenogram of the abdomen reveals pancreatic calcification is perhaps the most frequently encountered form. Such calcification may constitute the sole clinical evidence of chronic pancreatitis. Thus Gambill and Pugh[107] reported that in four of their twenty-nine cases of pancreatic calcification the patients had not had pain, steatorrhea or diabetes. Mayo,[112] in nine cases of pancreatic lithiasis encountered among 10,000 necropsies, found one in which there was no recorded history of pain or other symptoms.

Although pancreatic lithiasis may be encountered in the absence of other sequelae in cases of painless pancreatitis, more often steatorrhea and diabetes have also developed. In a series of ten cases of painless pancreatitis studied by Bartholomew and Comfort[111] steatorrhea and pancreatic calcifications were slightly more frequently encountered than diabetes. These workers commented on the interesting clinical feature of marked loss of weight in spite of an increased appetite in all ten patients. Recurrent jaundice and pseudocyst formation were less frequent complications, occurring in only three of the ten cases.

Equally intriguing from a diagnostic standpoint are the cases of painless chronic pancreatitis in which steatorrheal diarrhea is encountered in the absence of pancreatic calcifications, with or without diabetes. In such cases diagnoses other than chronic pancreatitis must be considered, including primary pancreatic atrophy, small ductal cell carcinoma or calculus blocking the duct of Wirsung, non-tropical sprue, Whipple's disease and the steatorrheal diarrhea complicating diabetes mellitus with neuropathy. Primary pancreatic atrophy and a small carcinoma blocking the pancreatic duct are differentiated only at surgical exploration, which also serves to give the patient the benefit of surgical treatment if early ductal carcinoma is present. Calculus occluding the duct of Wirsung is usually revealed in roentgenograms of the pancreatic region.[113,114] Non-tropical sprue usually is identifiable by the combination of steatorrhea with one or more of the deficiency states characteristic of sprue, including macrocytic anemia, hypoproteinemia with edema, hypocalcemia with osteomalacia and tetany, hypoprothrombinemia with bleeding tendency and other vitamin-deficiency states. Loss of excessive amounts of nitrogen in the feces does not serve to distinguish pancreatogenous diarrhea from that of non-tropical sprue. Whipple's disease may be suspected in cases simulating non-tropical sprue when one encounters middle-aged white men with antecedent migratory polyarthralgias and a generally downhill course, sometimes associated with fever, hives and a chronic cough. The diarrhea may or may not be bloody, but steatorrhea and azotorrhea are usually encountered. The abdominal pain in Whipple's disease is apt to be ill defined in nature and rather mild. Physical examination may reveal hypotension and hyperpigmentation and sometimes an abdominal mass. Peripheral lymphadenopathy occurs rather frequently in Whipple's disease and on histologic examination there are sometimes non-caseating granulomas suggestive of sarcoidosis. Whipple's disease is characterized also by elevation of the erythrocyte sedimentation rate and by the absence of macrocytosis in the peripheral blood. The diagnosis of Whipple's disease is established only upon histologic demonstration of the typical changes of macrophagocytosis of the tunica propria of the small intestine or lipogranulomatosis of the mesenteric lymph nodes, or both. The steatorrheal diarrhea complicating diabetes mellitus with neuropathy may be recognized by the history of long-standing severe diabetes with its complications of visceral and peripheral neuritis, and by the failure of the steatorrhea to be decreased upon administration of pancreatic extract.

To avoid abusing the diagnosis one must take care not to attribute mild and rather indefinite symptoms to painless chronic pancreatitis, especially in the absence of the sequelae of the disease. The diagnosis is definite, of course, if surgeon and pathologist have found unequivocal changes in the pancreas. The excellent response of patients with painless chronic pancreatitis to medical management serves to underscore the importance of the painful seizure as a therapeutic problem in the more frequently encountered form of chronic pancreatitis, in which pain is such a distressing symptom. Only the complications of diabetes mellitus remain real therapeutic problems in the patient with painless chronic pancreatitis treated medically.

THERAPY

Medical Management. Medical therapy has three objectives: first, palliation and termination

of the acute exacerbation; second, prevention of further seizures and pancreatic destruction; and third, control of external and internal pancreatic insufficiency— that is, of the steatorrhea and diabetes mellitus.[115]

For some years it has generally been thought that treatment of the acute exacerbations should be medical and that problems of management vary with the severity of the seizure.[5,53,115–117] Fortunately, in most cases the attacks are self-limited, subsiding after one or several days. When the seizure is mild—presumably due to edema of the organ, or at least with only small areas of necrosis—management may mean merely providing rest in bed, limiting the oral intake of fluids, and administering adequate sedation and appropriate fluids and electrolytes parenterally. In the more severe and prolonged episodes, in which pancreatic destruction is more extensive, attention must also be given to other problems, such as fluid and electrolyte imbalance; ileus with nausea, vomiting and abdominal distention; shock; and secondary infection.

Opiates presumably should be avoided initially because, by inducing spasm of the sphincter of Oddi, secretion of pancreatic juice into a closed-duct system raises the intraductal pressure, ruptures the ductal walls and adds to the degree of pancreatic damage. This consideration may be important in the attack only when the precipitating factors of food or alcohol are still present in the stomach in large quantities to stimulate pancreatic secretion. At any rate, drugs that presumably may control pain by relaxation of the sphincter of Oddi, such as glyceryl trinitrate (nitroglycerin) given sublingually in doses of 0.6 mg. ($\frac{1}{100}$ grain), or papaverine hydrochloride in doses of 0.13 gm. (2 grains), should be tried first. In deference to their theoretic danger, opiates, when given (and in practice they usually will be), should be administered along with drugs that suppress pancreatic secretion, such as atropine sulfate in doses of 0.6 mg. ($\frac{1}{100}$ grain) or ephedrine sulfate in doses of 25 mg. ($\frac{3}{8}$ grain) injected subcutaneously as often as every three hours; propantheline bromide in doses of 15 to 30 mg. may be given orally or intramuscularly at six-hour intervals. Continuous gastric aspiration likewise theoretically is of advantage, preventing entrance of the acid gastric contents into the duodenum and hence avoiding stimulation of the secretin mechanism.

In most attacks of five or more days' duration, in which fluids cannot be taken orally in adequate amounts because of nausea and vomiting, sensible and insensible losses of water and chloride must be estimated and replaced intravenously. The adequacy of replacement therapy often may be determined by the urinary output, by the degree of hydration of the tongue and skin and by the presence or absence of edema of the ankles; more accurate information being obtained by determination of values for blood urea, plasma chlorides and carbon dioxide-combining power of the plasma. When values for serum potassium fall below 3 to 4 mEq./L. one ampule of potassium chloride solution containing 1.49 gm. (20 mEq.) is given intravenously in a liter of fluid. The total amounts of potassium and chloride given per day depend upon the degree of depletion and upon the behavior of the serum values. Calcium gluconate in doses of 10 to 20 ml. of 10 per cent solution may be given when hypocalcemia appears.

Ileus and shock ordinarily respond to the usual methods of therapy. Continuous gastric aspiration and even intubation of the small bowel may be needed in order to decompress the bowel. Whole blood, human serum albumin and plasma volume expanders such as dextran are required to restore blood volume. The use of plasma is avoided ordinarily because of the danger of viral hepatitis. To explain the observed beneficial effect of administered serum albumin in combating toxicity and shock associated with acute destruction of the pancreas, an antitryptic effect was suggested.[118] However, the improvement following administration of albumin or blood is adequately explained by restoration of normal blood volume.[119] Cortisone, hydrocortisone and their analogues have been advocated not only in the management of shock but also because of their anti-inflammatory effect. However such therapy is difficult to evaluate in a disease as self-limited as is the acute exacerbation of pancreatitis.

Chlortetracycline (aureomycin®) or oxytetracycline (terramycin®), orally when possible, after ingestion of milk, should be given in doses of 500 to 750 mg. every six hours when moderately high fever appears, especially if of septic type. If antibiotics cannot be taken orally, penicillin procaine in a dose of 1,000,000 units and 1 to 2 gm. of dihydrostreptomycin can be given intramuscularly each day, or 500 mg. of chlortetracycline or oxytetracycline in 200 ml. of isotonic saline solution may be given intra-

venously twice daily. Hyperglycemia and glycosuria may appear during acute episodes and will require proper management.

Following cessation of the painful seizure, medical means to prevent, in so far as possible, recurring painful seizures and progression of the disease are few and of limited value. Adherence to a bland diet, avoidance of overeating and complete abstinence from alcohol are the most important measures.

Control of pancreatic insufficiency, developing as destruction of the pancreas progresses, requires control of diabetes and of excessive losses of fat and nitrogen, with their associated abdominal discomfort and loss of weight. Steatorrhea and azotorrhea may be controlled satisfactorily by a dietary program and by the use of pancreatin. Caloric losses may require a caloric intake greater than normal, at times as much as basal plus 70 or 80 per cent. Because the greater the intake of fat and nitrogen, the greater the absorption of these foodstuffs, the simplest method of combating excessive losses is ingestion of fat and nitrogen in amounts greater than those usually consumed by normal persons. Large amounts of protein are well tolerated but large amounts of fat may well increase the diarrhea and abdominal discomfort. Consequently, the dietary intake of fat usually is restricted to 50 to 70 gm. a day, with ingestion of 120 gm. of protein and up to 450 gm. of carbohydrate to compensate for the calories lost by restriction of fat intake. Concentrated triple-strength pancreatin as enteric-coated tablets (0.3 gm., or 5 grains, in each) is given in effective doses. Pancreatin in doses up to 5 gm. with each meal is sometimes necessary to reduce significantly the fecal losses of fat and nitrogen, to permit the ingestion of fat in amounts sufficient to make the diet palatable and to reduce abdominal discomfort. Sometimes much smaller doses are effective; the patient usually can best determine his own effective dose. The amount of insulin required may be increased by the efficient use of pancreatin. A multivitamin capsule will provide adequate vitamin supplements, especially needed when the patient is malnourished and the intake of food is restricted. Anemia may require iron compounds orally or intravenously or whole blood by transfusion.

Surgical Treatment. The large number of surgical procedures employed in the treatment of chronic pancreatitis reflects the continued efforts, too often unsuccessful, to prevent progression of the disease and to prevent and relieve pain.[53,115,116] In many cases the physician and surgeon must be willing to settle for temporary relief, even partial palliation, always with the hope that the disease eventually will become quiescent.

The surgical procedures employed in the treatment of chronic pancreatitis may be divided into several groups.

Procedures for removing disease of the biliary tract are used not only to relieve symptoms due to disease of the biliary tract and to prevent complications potentially hazardous to the patient but also to remove a disease so frequently associated with pancreatitis and, it is widely believed, capable of precipitating acute episodes and progressive destruction of the pancreas.[12,53,116] The removal of a normal-appearing gallbladder in the treatment of chronic pancreatitis has not been helpful in preventing recurring attacks. Not infrequently, acute pancreatitis fails to recur following removal of disease of the biliary tract in patients in whom the pancreatitis has obviously appeared as a complication. In such cases it is possible that the pancreatitis may be fundamentally different in some respects from the recurring painful seizures of chronic relapsing pancreatitis. Chronic pancreatitis in the case of stone in the common duct with jaundice neglected over a period of years may likewise subside following removal of the stones from the duct. Removal of disease of the biliary tract in the well established case of chronic relapsing pancreatitis, however, although sometimes followed by relief, fails all too often to affect the frequency and severity of the attacks.

External and internal drainage of the common bile duct are commonly employed to reduce pressures in the common and pancreatic ducts in the presence of a common channel, believed perhaps to favor subsidence of the acute changes in the pancreas and surrounding structures, in turn tending to relieve obstructive factors in the ampullary region.[53] Cholecystostomy, one of the earliest procedures of this type, is not recommended today, even though in the occasional case relief from the painful seizures has followed. Prolonged external drainage of the common bile duct by use of a T tube[24,120–125] has the disadvantage of not providing permanent drainage. Internal drainage,[44,126,127] if permanent, is theoretically superior. Various types of internal drainage have been employed. Among them

may be mentioned side-to-side anastomosis between the gallbladder and the stomach or jejunum, side-to-side anastomosis between the common bile duct and duodenum or Roux-Y type of anastomosis between the gallbladder and the jejunum.

Priestley and associates[53] have recently reviewed the results of external and internal biliary drainage in 100 cases of chronic pancreatitis in which there was definite and clear-cut evidence of the existence of the disease both clinically and at surgical exploration. External biliary drainage in seventy-two cases gave complete relief in 52 per cent, partial relief in 22 per cent and no relief in 26 per cent. Internal biliary drainage, usually by means of side-to-side choledochoduodenostomy, was employed in twenty-eight patients and afforded complete relief in 39 per cent, partial relief in 39 per cent, and no relief in 22 per cent. Although the series of cases was not large, the results are more significant because the follow-up period was five to nineteen years in two thirds of the cases, and three to five years in one third. Better results were obtained when disease of the biliary tract was present and before the sequelae of pancreatitis had appeared.

Sphincterotomy, first advocated some forty years ago by Archibald[45] and currently in wide use, largely due to the impetus given by Doubilet and Mulholland,[11,48,54,117,128–133] is employed to relieve spasm of the sphincter or inflammatory obstruction in the ampullary region. Doubilet and Mulholland's[54] experience over eight years has been highly satisfactory. The course of the disease was thought to have been reversed in 173 of the 190 patients in whom endoductal or transduodenal sphincterotomy was carried out. The results were poor in four patients and failures occurred in seven. There were nine deaths. The procedure has been followed by disappearance of pancreatic pseudocysts and fistulas.

The results of sphincterotomy in the hands of our surgical colleagues[53] has been somewhat encouraging but follow-up studies covering periods of more than five years are not yet available. To date one third of fifteen patients have obtained complete relief and another one third partial relief from the attacks of pain. These results to date are similar to those obtained with external and internal biliary drainage.

Operations on the pancreas itself include procedures such as removal of pancreatic calculi (followed by T-tube drainage) to relieve pancreatic ductal obstruction, marsupialization and prolonged external or internal drainage of pancreatic pseudocysts, and partial and complete pancreatic resections.

Removal of large stones from the main pancreatic duct[134,135] has been followed by good results in a limited number of patients, especially when the stones seem to be largely intraductal. Surgical drainage of pancreatic pseudocysts[136–142] by and large has been successful; in some cases drainage of the cyst has even been followed unexpectedly by partial or complete cessation of painful seizures. Internal drainage of pancreatic cysts is preferred to external drainage because of the unpleasantness of prolonged external drainage.

Partial or complete resection of the pancreas is considered only after more conservative measures have failed and only when disability is marked, because of the higher mortality rate and the resulting morbidity from these procedures. Partial pancreatectomy so carried out that external pancreatic secretion from the remainder of the gland drains into the gastrointestinal tract, thus preventing in so far as possible maldigestion and malabsorption, is preferred by the physician and the patient. The results of partial pancreatectomy[120,135,143,144] to date have been gratifying, and in some cases, but not all, this has been true when partial resection was limited either to the head, or to the tail and perhaps body, of the pancreas. Total pancreatectomy[135,143,145,146] has been employed only in the exceptional case in which all previous measures have failed.

Procedures designed to decrease pancreatic secretion are partial gastrectomy, vagotomy and sympathectomy. They have been employed infrequently, in the belief that pancreatic secretion aggravates pancreatitis by increasing intraductal pressures.

After partial gastrectomy, failures have been reported,[116,147] as well as some good results,[148,149] over short periods. We have not seen the course of the disease halted when partial gastrectomy has been carried out for a concomitant duodenal ulcer. Vagotomy alone has been followed by improvement in a few cases,[147] and relief by transthoracic vagectomy and sympathectomy for a period of ten months has been reported.[150] Failures also have been reported.[151] By and large, this group of procedures seemingly has not offered much to the patient. The possible addi-

tion of untoward postvagotomy symptoms to those of chronic pancreatitis has doubtless detracted from interest in this procedure.

Sympathectomy[135,150–158] for relief of pain is important when other measures have failed and when pain is frequent or constant and disabling. In our experience, relief of pain is somewhat unpredictable and may be only partial. Ordinarily such relief lasts for only two to three years; to date no patients have experienced relief lasting more than five years. Despite the temporary character of the relief, sympathectomy is justified in selected cases, preferably after the disease has been established by abdominal exploration and biopsy and also after procaine and alcohol blocks have produced appreciable temporary relief.

A number of variables complicate appraisal of the results of surgical therapy. Not uncommonly the process seems to become quiescent spontaneously and remissions may last for long periods. Even the number and the severity of the attacks may vary greatly. Adequate study of the natural history of the disease has not been recorded, nor do we know the percentage of cases in which spontaneous remissions occur. Other variables are the presence or absence of disease of the biliary tract, the effect of previous operations, the stage of destruction and activity of the disease in the pancreas, and the presence or absence of diabetes, calcifications, pseudocysts or external pancreatic insufficiency. The results of therapy to date leave much to be desired. They compare poorly with the results obtained, for instance, by the removal of disease of the biliary tract for its own symptoms, or for partial gastrectomy for duodenal or gastric ulcer. Nevertheless, until a more definitive form of therapy is available the physician has no choice but to ask the surgeon to carry out those procedures which seem appropriate in the individual case to provide palliation and prevent further pancreatic destruction and invalidism.

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Conference on Therapy

Treatment of Diseases of the Eye Seen in General Practice

THESE are stenographic reports, which have been edited, of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and the New York Hospital, with collaboration of other departments and institutions. The questions and discussions involved participation by members of the staff of the college and hospital, students, and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

DR. GEORGE READER: A conference on diseases of the eye seen in general practice appeared in the first volume of the Cornell Conferences on Therapy. Since then there have been many advances in management and we thought it would be useful to have Dr. McLean bring us up to date.

DR. JOHN M. MCLEAN: I looked up the conference which was published in the first volume some time after it was originally given, over ten years ago, and I was amazed at the change in therapeutic agents in the past decade. General principles are essentially unchanged but the agents that we use today are very different from those we had ten years ago. When that conference was given, some of the sulfonamides which are now available were not in use, some that we use most commonly today were not yet to be had; penicillin had not appeared. If you review that conference you will see that between the time it was given and the time it was published penicillin had appeared, and it was necessary to insert a few editorial comments here and there concerning the possible value of penicillin.

As I looked through the list of agents which we mentioned, I jotted down a few things which we were using ten years ago, all of which were in the Pharmacopoeia, most of which were in that little book called "Useful Drugs," and many of which now belong on my private list of useless drugs. They include such things as boric acid, mercurous and mercuric oxide, bichloride of mercury, arsenicals, ethylmorphine (dionin) and ethylhydrocupreine (sometimes known as optochin), all without sound application today. In addition, a mild silver protein known as argyrol was prominently mentioned; today we believe it has no function except a mechanical one in helping to visualize and agglutinate the mucoid discharge to simplify the mechanical irrigation of the conjunctival cul-de-sac. In the past ten years the advent of antibiotics and of adrenal hormone therapy has revolutionized therapy, and at the same time has further tempted the general practitioner to try to treat more and more eye diseases. The ophthalmologist sometimes gets very irritated at some of the things the general practitioner does to eyes, with the best of intentions and the worst of results. When penicillin became available it seemed as if almost every general practitioner was going to put penicillin in a patient's eye and see if it worked. If it did not, he would then call for help. That has broadened, now, to include the use of many other newer medications. It seems as if general practitioners still peer into the eye, pour a little cortisone into it, and if that does not work send the patient to the ophthalmologist. We get very irked at this blanket, illogical, shotgun approach, and are most unhappy when we see irreparable damage done by the improper use of these agents, and by delay in the institution of suitable therapy; for example, the treatment of acute glaucoma and acute uveitis as conjunctivitis.

In any discussion of ophthalmologic therapy in general practice the most important thing to mention is the group of acute emergencies which the non-ophthalmologist may have to meet on the spot without having time to get expert advice. Probably the most serious and most acute of these is the group of caustic chemical burns which require prompt therapy. Here we repeatedly see that a physician on the spot at the time

of the injury thinks back to his training as a Boy Scout rather than to his training in ophthalmology and wastes valuable time trying to decide whether the chemical burn was alkaline or acid. Of course the thing he should do without worrying about pH or chemical identification is to remove the irritant chemical immediately by copious irrigation of the eye with the first convenient irrigant available. More often than not it is tap water or lake water; if it happens to be in a hospital emergency room, it may be normal saline solution or the equivalent, but time taken looking for a neutralizing agent is really time wasted, particularly if it is an alkaline burn.

After the irritating chemical has been thoroughly washed out, and after the cul-de-sacs under the lids have been explored for any particulate chemical matter, one can sit back and wonder whether it was an alkali or an acid that caused the burn. That is important in one respect only: acid burns are usually complete in their damage almost immediately, whereas alkaline burns, which penetrate the cornea so readily, are almost always worse the next day no matter how severe or how mild they may look at the time of injury. It is therefore important to follow carefully even a mild alkaline burn and it is impossible to assess the total amount of damage at the time of first aid. When the chemical burn is caused by calcium compounds such as lime, which is a common one, the cornea is penetrated and calcium precipitates in the depths of the cornea after a short time and may cause considerable permanent damage. Much of this can be avoided after irrigation by the prompt use of neutral ammonium tartrate, but that is rarely on hand at the moment of the accident.

In addition to chemical burns, some of the common emergencies are essentially surgical: perforating wounds and some of the serious nonperforating wounds. There I think the best thing the man who is not equipped to render definitive treatment can do is simply to put a sterile dressing over the eye, keep his hands out, and bring the patient without trauma to some site where good definitive treatment can be rendered. Most of the meddling surgical first aid to the eyeball does more harm than good.

A third group of acute emergencies is the vascular group, the more acute of the two types of course being the arterial occlusions, particularly sudden occlusion of the central retinal artery, which may be the result of an embolus or a spastic closure. In most of these instances treatment is not successful but it is helpful in a sufficient number to justify rigorous, prompt attempts in every case. You must remember that immediately after a central arterial occlusion the cherry red spot which you have read about in your textbooks and heard about has not yet developed. You simply see empty threadlike vessels and slight pallor of the fundus. At that point, everything which can be done to dilate the patient's retinal arterial circulation should be done. Unfortunately, complete evidence as to the effectiveness of various dilators is not yet available. It is customary to use such agents as amyl nitrite, nitroglycerine and the other nitrites promptly, although the evidence in their favor is somewhat equivocal. It is also customary to use such agents as intravenous nicotinic acid and, in recent years, there has been some fairly good evidence that anoxia or at least hypoxia and high carbon dioxide concentration in the blood will produce some vasodilatation. The most efficient immediately available method for producing this combination, of course, is rebreathing. These methods are not, however, always successful.

In addition, when it can be done, the pressure surrounding the retinal vessels should be relieved by decompressing the eyeball by paracentesis of the anterior chamber. Further efforts to dislodge an embolus should include rather vigorous massage of the decompressed eyeball. A few years ago I saw a dramatic example of this combination in a patient who happened to be a physician and who was practicing in upper New York State some miles from New York City. He suddenly went blind in one eye. He was seen by a colleague in his small town who immediately made the correct diagnosis—his colleague was an ophthalmologist—of a central retinal arterial occlusion but, because of some confusion, instead of instituting therapy on the spot the patient was put on a plane for New York. The weather happened to be bad, and the plane happened to be unpressurized, and it was necessary for the pilot to go to rather high altitudes to get above the storm. The patient lost consciousness for a while from lack of oxygen. When he came down at LaGuardia Airport his central artery had opened up, the central circulation was restored, and he was seeing again—all of this a beautiful but completely accidental experiment. When he arrived, he was cured. The sad part of the story is that some months later the same thing happened to the same man in the same town. They

went through the same maneuvers without benefit of bad weather, and this time were unsuccessful, and he has been blind in that eye ever since.

Occlusion of the central vein is somewhat less of an emergency but is still a serious vascular accident. Statistics to date indicate that the intelligent use of anticoagulant therapy over a period of many weeks after central venous occlusion is worthwhile. We used to feel that heparin was distinctly superior to dicumarol but now we believe that if dicumarol dosage is managed efficiently, it is just as effective. Heparin has the one advantage of initiating its effect a little more promptly and we sometimes start a patient on dicumarol and heparin together, stopping the heparin as soon as the dicumarol takes effect.

In the last therapy conference we held on this subject we spent a lot of time on external infections: the common sty, hordeolum, lid abscess, conjunctivitis and chalazion, which is a retention cyst of the meibomian gland. The entire problem can be simplified today by saying that if the infection is serious, it had best be treated at the onset by one of the wide-spectrum antibiotics such as terramycin® or aureomycin® ointment used locally. Bacteriologic studies should be started at once and the therapeutic regimen subsequently adjusted, depending on the sensitivity tests made on the organism recovered at culture. There are, for example, some particularly serious corneal infections; those produced by pyocyaneus are among the most devastating. Most strains of this organism in the eye are more susceptible to polymyxin B locally than to any of the other agents we have. That, however, is not true of all strains of this organism, and the therapeutic agent should be fitted as soon as possible to the bacterial sensitivity tests made in the laboratory. Until exact information is available, the best broad-spectrum antibiotic should be used. But I should add a word of caution on this subject because there is a great tendency, in the treatment of minor and unimportant surface infections, to load the patient with antibiotics to which he may become sensitized. It is not worth while to sensitize a patient to an agent which might be life-saving at some future time in order to treat an unimportant conjunctivitis. In such cases I believe that, whenever possible, the agent of choice should be one of the effective antibiotics which can be used locally in the eye but which has little or no systemic application, such as neomycin, bacitracin, gramicidin, and the like. These are highly effective in many superficial eye infections where they can be used locally but are of little potential use systemically if the same individual should some time require major antibiotic therapy. Of course we should always mention, in conjunctivitis, corneal ulcers and other external infections, the importance of examining the lacrimal sac, for it does little good to treat the conjunctiva or the cornea if it is constantly being reinfected from a pool of bacteria in the patient's lacrimal sac. All too often therapy fails because of failure of the physician to look for this source of constant reinfection.

As to the various inflammations, we can say in a broad general statement that most ocular inflammatory disease responds to adrenal hormone therapy. A majority respond to the local use of cortisone or hydrocortisone. Most all of these, and some others, too, respond to the systemic, particularly the intravenous use of corticotropin or ACTH. Do we necessarily want to use them in all cases? If the inflammatory manifestation is allergic, yes. It can almost always be suppressed by such therapy and the patient will be greatly benefited without doing any harm. If these inflammatory responses are in the nature of acute self-limited inflammations which will do tissue damage to the eye, the inflammation can be suppressed. Damage can be lessened or prevented until the episode has passed, and then the therapy can be withdrawn. Are we right in suppressing inflammation in the presence of bacterial infection? I think not, unless we combine with this adequate specific antibiotic therapy to control the source of infection. If we do not do so we are simply suppressing the manifestations of disease. We are allowing the course of the disease to run unchecked and lulling ourselves and the patients into a false sense of security which will be completely reversed when we withdraw the suppressing agent and are faced with an overwhelming infection. There is, moreover, considerable doubt as to the advisability of using these agents in many of the granulomatous infections of the eye unless specific therapy against the inciting agent can also be used. If it can, then it may be worth while to suppress the tissue damage from the inflammatory reaction. If it cannot, we are suppressing the host defense against the noxious agent and are simply alleviating symptoms tem-

porarily, allowing the inciting agent to develop unchecked and preventing the body from forming its own defenses. The end result is an overwhelming relapse or an unusually serious subsequent recurrence.

As we look again at the conference given ten years ago we find a number of other more or less miscellaneous items. There were questions then, and there may be questions now, about prophylaxis in the eyes of the newborn. At that time we said rather didactically that the only safe form of prophylaxis was the use of 1 or 2 per cent silver nitrate in the eyes of the newborn. That is still the only acceptable form under the laws of most, though not all, states. Some give more latitude. There is experimental work under way in this institution and in a number of others, which has been going on for twenty years, stimulated by the occasional chemical burn, not too serious, produced by silver nitrate. As yet, most of the statistics are not completed sufficiently to come to a final conclusion. Tentatively we can say that a number of other prophylactic agents, such as local penicillin ointment, intramuscular penicillin in the mother six hours before delivery, the local use of aureomycin and terramycin, all seem to produce as effective a prophylaxis as silver nitrate. All seem to do so without the local irritation of the baby's eyes caused by the silver nitrate but there is no conclusive proof that any one of them is superior as a prophylactic agent. There is, too, the potential danger of infection with gonococcus strains which may be resistant to the particular antibiotic used, whereas we know of no gonococcus in the newborn baby's eyes which is resistant to silver nitrate. Until these agents can be definitely shown to be superior, I think we should routinely rely on the tried and true silver nitrate prophylaxis.

Occasionally we hear of silver protein prophylaxis in the newborn baby's eyes. I have nothing to say about that except to condemn it as grossly inadequate.

There were a number of questions ten years ago about the best agents for the general practitioner to use for routine mydriasis for ophthalmoscopic examination. There is not much change in that situation. We use adrenergic drugs a little more commonly than we did then, usually phenylephrine in strengths from about 2 to 5 per cent. Many of you know that drug better under its trade name of neo–synephrine.®

There were questions ten years ago about local anesthetics. The answer then gave tetracaine, which many of you know under the trade name of pontocaine,® as the agent of choice, in 0.5 to 1 per cent concentrations. This is still essentially correct, but we now have holocaine, cocaine and a number of others available as substitutes.

At the end of the conference ten years ago I made a few remarks directed to and at some of the general practitioners. I likened the treatment of glaucoma to the treatment of diabetes, comparing the non–surgical treatment of glaucoma to the dietary control of diabetes and comparing the surgical treatment of glaucoma to insulin therapy in diabetes. I reminded them that glaucoma, like diabetes, is a disease which may be controlled but is never cured, and which requires constant supervision through the rest of the patient's life.

On the subject of cataract I simply tried to remind those present that many of them had been brought up on the notion that a cataract had to be mature before it could be operated upon. Ten years ago, and even more so today, that notion is just as wrong as it can be. A cataract can be extracted by modern surgical means at any stage of its development and should be operated upon whenever the patient's visual handicap requires it, regardless of its state of anatomic development.

It is always in order to remind pediatricians that strabismus in the child requires early ophthalmologic consultation, preferably by the age of two. The advice sometimes given to wait until the child grows up or to wait until the child can be operated on under local anesthesia before consulting an ophthalmic surgeon may result in permanent damage to the child, to his personality and to his visual efficiency.

I think that covers most of the things we mentioned in the similar conference years ago, with an attempt to bring some of them up to date.

DR. READER: Thank you, Dr. McLean. Are there any questions?

DR. SIDNEY ROTHBARD: I wonder if it would be too much trouble to give us again the therapy for occlusion of the central retinal artery? I did not quite get that point. It seemed to me that the point was to reduce oxygen tension, if possible, in the hospital. How would you go about doing that?

DR. MCLEAN: You do that by rebreathing into a bag, which is a common nursing procedure in all hospitals. You can use an anesthetic mask with a closed system, removing some of the oxy-

gen supply from the patient and supplying him with something else.

DR. ROTHBARD: How much carbon dioxide?

DR. MCLEAN: I would get a competent anesthesiologist and leave the technical details to him. If forced to do it on my own without an anesthesiologist, I would rely upon simple rebreathing which will quickly exhaust the patient's oxygen supply. I would try to stop somewhere short of fatality.

DR. READER: How long do you keep that up?

DR. MCLEAN: As long as you safely can.

DR. READER: Do you give anticoagulants?

DR. MCLEAN: There is little rationale for anticoagulant therapy in an acute arterial occlusion because if the occlusion cannot be relieved in a very short space of time, measured usually in minutes, certainly in an hour or so, it is of no avail to relieve it, and I do not know of any anticoagulant that takes effect that fast. If, however, the occlusion can be relieved, then there may be some virtue in subsequent anticoagulant therapy in hopes of preventing reformation of the occlusion. This is in contrast to venous occlusion in which time is less important and anticoagulant therapy is worth while.

DR. ROTHBARD: Is there any experience with the peripheral vascular dilators in this ailment?

DR. MCLEAN: Such as priscoline®?

DR. ROTHBARD: Yes, have those been tried?

DR. MCLEAN: The experience with them in the retinal circulation is very scanty. Most reports are either equivocal or discouraging.

VISITOR: Would you say that a child with strabismus should be operated on by age two?

DR. MCLEAN: No, I did not mean to imply that at all. I was suggesting that the ophthalmologist ought to see the child at least by age two. If the strabismus is a common strabismus, there is not going to be much he can do before that age. He may not want to do much at that time, but he may. That decision should rest with him, not the pediatrician or the general practitioner. On the other hand, if the strabismus is extreme, or if it has a severe paralytic element in it, he may want to operate early, as soon as he can make an accurate diagnosis. At the same time, I do not want to suggest that every newborn baby be sent to an ophthalmologist because its eyes wander. All newborn babies' eyes wander.

DR. READER: I imagine the pediatrician will be able to make that differentiation?

DR. MCLEAN: Yes.

DR. READER: What about foreign bodies in the eye? You did not tell us when a foreign body in the eye becomes too big a problem for the general practitioner.

DR. MCLEAN: That depends more on the availability of the ophthalmologist than anything else. A simple foreign body resting on the surface of the conjunctiva or the lid can be safely removed by almost anybody with a steady hand using a clean cotton applicator. A foreign body resting on the surface of the cornea can be similarly wiped off without doing damage, but by and large I think the general practitioner will find himself in trouble more often than not if he attempts to anesthetize the eye and dig an imbedded foreign body out of the cornea. There he will do better to patch the eye, perhaps put in an ointment, or if pain is severe, an anesthetic ointment, and refer the patient to someone properly equipped to remove it. Eyes have been punctured altogether too often by ill advised attempts to remove imbedded foreign bodies with small sharp instruments. Also, this is probably the place to remind you that every once in a while a general practitioner gets hold of a small sharp instrument, a needle or a knife, and digs a big ulcer in the cornea trying to remove a small mole in the iris which he thinks is a foreign body on the cornea. That is usually the result of improper equipment for examination.

DR. READER: What about emergency treatment of a penetrating wound of the eye?

DR. MCLEAN: As I suggested, I think if it is at all feasible the eye should simply be covered by a sterile dressing and the patient transported with as little trauma as possible to a place where adequate, definitive treatment can be given. Crude attempts at suture repairs and at the removal of penetrating foreign bodies usually do more harm than good.

DR. READER: What about prophylactic antibiotics for a patient of that sort?

DR. MCLEAN: If there is going to be an important time lag before the patient can be gotten into proper hands it is probably worth while to give him systemic prophylactic antibiotics. It should also be mentioned that the eye is a good portal of entry for tetanus, and tetanus entering through the eye usually produces that most serious form known as cephalic tetanus, so if there is going to be a significant time lag the patient should have proper prophylaxis against tetanus as well as antibiotics. If the eye is perforated and softened, most of the antibiotics,

aureomycin, terramycin, penicillin and the like, will enter the eye in sufficient concentrations. If the eye is not seriously softened many of these agents will not enter the globe from systemic administration in adequate concentration but chloramphenicol given systemically will, and is probably the best over-all antibiotic for such purpose.

DR. READER: How about the management of the patient with detachment of the retina by the physician who first sees him?

DR. MCLEAN: The first thing the ophthalmologist does almost invariably is to put that patient flat in bed, but the minute his position is changed everything gained by that bedrest, which may have been hours or weeks, is lost; bedrest for a period of time followed by getting the patient up to transport him is wasted time. It is better to transport him right away and start his bedrest in a location where he will be able to maintain it until the operation is instituted.

DR. READER: I noticed there were several drugs mentioned in the previous conference that you did not refer to today either disparagingly or otherwise, such as zinc sulfate. Do you still use it?

DR. MCLEAN: Zinc sulfate has two uses today. It is still a safe, mild astringent and still useful for that purpose. Nowadays we do not need astringents in the eye as much as we used to because in most instances we are able to do something more specific about the cause of the irritation for which we were using palliative astringents. Zinc sulfate also has a specific use in angular conjunctivitis, which is caused by the Morax-Axenfeld bacillus. Here the symptoms and the distress are caused not by the bacillus itself but by the proteolysis produced by the bacillus. The presence of zinc ion will completely inhibit the enzymatic action of the bacteria, and any ionizing preparation of zinc will alleviate those symptoms until the host has had a chance to overcome the organism. Zinc sulfate is usually the safest and most comfortable form. Zinc chloride is just as effective but much more painful.

DR. READER: Do you think there is any use for butyn sulfate?

DR. MCLEAN: I do not believe butyn is used very much any more. It is an adequate surface anesthetic but the incidence of development of tissue sensitivity to butyn is so much higher than to a number of the other surface anesthetics that it has been pretty much discarded. It is a perfectly adequate anesthetic but produces too many cases of drug sensitivity.

DR. READER: How about the antihistamine drugs? Do you use them for the irritation associated with hay fever or allergic reactions around the eye?

DR. MCLEAN: The antihistamine drugs are still used in the eye locally. At the moment their use is falling off rapidly in favor of the use of local cortisone or hydrocortisone.

DR. READER: Do you have any preference for one antihistamine over another?

DR. MCLEAN: No, there are several which are about equally effective, and in one patient and one situation, one seems to work, and in the next patient and another situation another seems to work better. It is pretty much trial and error.

DR. MYRON A. BUCHMAN: Is there any treatment for an acute radiation burn of the eye?

DR. MCLEAN: That depends on the radiation burn. There are several different types. Will you tell me what you mean?

DR. BUCHMAN: An x-ray burn in case of any atomic attack in which eyes might be affected in a specific person.

DR. MCLEAN: No, there is not much to be done in that type of radiation damage. In the first place, most patients under ordinary circumstances that are exposed to enough radiation to produce serious ocular damage have enough general body radiation to be killed. The most serious ocular damage from that type of radiation is the delayed production of radiation cataract. I know of no successful therapy in the human for that. There are some interesting animal experiments that have been done by von Sallmann which so far are only applicable to the mouse and the rat. It may be developed into something of use to the human.

If you are referring to such things as ultraviolet burns, which are characterized by their latent period, usually eight to twelve hours, followed by severe surface pain, photophobia and copious lacrimation caused by the delayed damage and sloughing of the corneal epithelium, the only thing necessary is alleviation of the acute distress of the patient because the epithelium will repair itself perfectly well. A few drops of a mild local anesthetic are usually all that is required to keep the patient comfortable until his epithelium repairs, which it will do in from twelve to twenty-four hours.

DR. READER: A homely problem that many general practitioners face from time to time is the

black eye. Dr. McLean, is there any good treatment for black eyes?

DR. MCLEAN: No.

DR. THOMAS ANDERSON: Do you recommend any treatment for the conjunctivitis seen in measles in the acute stage?

DR. MCLEAN: Usually, nothing is required in the conjunctivitis of measles but cleanliness and sufficient protection from light to make the patient comfortable. I know of no evidence that exposure to light does any damage to the eye in the presence of measles conjunctivitis, although it is a common idea that these patients should be kept in dark rooms. Inasmuch as they have some photophobia, they should be sufficiently protected from light to be comfortable, but further darkening is unnecessary. The discharge should be cleansed away with any mild irrigating solution such as normal solution of sodium chloride, and they usually heal by themselves.

DR. ANDERSON: Their accommodation should not be paralyzed?

DR. MCLEAN: I see no reason for it in conjunctivitis. If a true measles virus keratitis develops, which is another matter, it may be worth while to try paralyzing accommodation. Measles, in common with all virus keratitis, probably should not be treated with adrenal hormone locally or otherwise. Evidence is accumulating that virus infections of the cornea by and large are made worse by the use of cortisone and such agents, although there are definitely some conflicting reports in the literature.

DR. READER: Are there any antibiotics that you would use for virus infections of the eyes other than trachoma?

DR. MCLEAN: It is worth while to use antibiotics against secondary bacterial infection, and there are a few of the large-particle viruses such as trachoma, which borders on Rickettsia, in which aureomycin and terramycin seem to be worthwhile, but the true small-particle viruses do not seem to be affected by antibiotics.

DR. READER: Dr. Gordon, do you have any comments on possible areas we have skipped in the eye diseases?

DR. DAN M. GORDON: Dr. McLean has hit the high spots. I think his dictum that if you cannot do the patient any good, don't do him harm by keeping him from adequate treatment, is a logical one. Also, if it can be avoided, one should not treat a patient without a diagnosis. That is one way of getting into trouble. The general practitioners and students always ask when a non-ophthalmologist should get his patients to the eye doctor. I think two of the most important conditions are: first, any condition which causes a disturbance in vision; second, pain in the eye not due to some grossly visible cause such as a foreign body. The biggest mistake is made in treating painful or semi-blind eyes due to glaucoma or something of that sort, usually an emergency condition, beyond the time when an ophthalmologist could help. We are all disgusted when we see patients like that because then we are helpless. I have one right now, a patient with severe uveitis, that the general practitioner treated for several weeks with cortisone eye drops. I have been treating him for over a month for a condition which I am sure would have responded in a few days had he been adequately treated in the first place.

I am glad Dr. McLean mentioned strabismus. Here, again, the same dictum applies. If advice is considered part of therapy, do not give the patict bad advice. The most common bit of bad advice in strabismus is, do not bother having an eye doctor see the child because he may grow out of it. Very few children do.

DR. READER: Since Dr. Gordon mentioned diagnosis, I wonder if you could summarize briefly the kind of diagnostic examination a general practitioner should give a patient who comes in with an eye complaint.

DR. MCLEAN: In the three minutes remaining I do not think we can do that. We try in three years to explain it to the medical students.

DR. READER: There must be some relatively simple routine that most general practitioners follow. What do you think they generally do? We have left that out and it is important. What do they generally not do that they should do?

DR. MCLEAN: I think the first thing they leave out that is important is some attempt to assess the patient's vision either with or without his glasses. That can usually be estimated in one way or another. I believe that the general practitioner should have some sort of visual testing chart in his office both for distant and near vision. If he has not, he has a newspaper or a telephone book and from it can see if the patient can read fine print.

Frequently the general practitioner fails to look at the optic nerve before using mydriatics to dilate the pupil. Every once in a while we are called in a hurry by a panicky practitioner who

could not or did not attempt to see the eye grounds until after he had dilated the pupil and then discovered that the patient had chronic glaucoma. I have not been called in a problem like that now for nearly ten days, but that is a long lapse; usually it happens more frequently. Almost anybody who can use an ophthalmoscope at all can at least see the nerve head through the undilated pupil, and if it is cupped, he had better not dilate the pupil. I do not have much faith in the ability of the general practitioner to estimate the intraocular pressure with his fingers. I think all of us who are doing it very many times a day every day are more unsure of our finger estimates than the amateur is of his; the fact that a general practitioner tells me, "Well, I felt this patient's pressure with my fingers and I knew it was normal," does not mean a thing to me.

Another common mistake is omitting to differentiate between conjunctival injection and circumcorneal injection of the blood vessels. The first indicates a surface involvement and the second an intraocular involvement of one type or the other, and almost always requires specialized attention. It cannot be treated as a conjunctivitis. I think those are perhaps some of the outstanding points.

SUMMARY

DR. SOLOMON GARB: During the past decade there have been many changes in therapeutic agents used in the treatment of eye diseases, but not in basic principles. The first principle is that the general practitioner should not attempt to treat conditions which require the skill and training of the ophthalmologist. It is advisable to refer the patient to an ophthalmologist at once when there is any disturbance in vision or pain in the eye not due to an easily removable foreign body. The general practitioner should not try to remove imbedded foreign bodies. Attempts to treat eye conditions with antibiotics or adrenal cortical hormones before establishing a definite diagnosis may cause irreversible damage. There is a group of emergencies which require immediate treatment by the first doctor to see the patient. They include caustic chemical burns, some injuries and vascular accidents. The methods of handling these situations by the general practitioner were discussed. The proper use of antibiotics and adrenal-cortical hormones was described. Early consultation for conditions which might require surgery, such as strabismus in babies, and cataracts, was advocated. The precautions indicated in routine mydriasis were emphasized.

Clinico-pathologic Conference

Myasthenia Gravis with Acute Chest Pain

STENOGRAPHIC reports, edited by Amoz I. Chernoff, M.D. and W. Stanley Hartroft, M.D. of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient (No. 105673) a white business man, eighty-four years of age, was admitted to the Barnes Hospital for the first time on May 28, 1943, and died during his second admission on January 9, 1956.

The patient gave a history of having had fatty food intolerance for several months prior to his first admission. For six weeks he had had almost constantly a dull, aching pain in the right upper abdominal quadrant, with exacerbations following meals. For one week prior to admission he had noted dark colored urine and the appearance of yellow scleras. The vital signs were normal. The patient appeared mildly icteric. The remainder of the physical examination was normal except for moderate tenderness in the right upper abdominal quadrant. The liver was not palpable. Laboratory data revealed a normal hemoglobin, white blood cell count and differential count, and a normal urinalysis. Hepatic function tests: normal cephalin cholesterol flocculation test and thymol turbidity; alkaline phosphatase 10 Bodansky units; total bilirubin 6.5 mg. per cent with equal amounts of direct and indirect reacting pigment.

After a one-week period of observation the jaundice did not subside and the hepatic function tests remained the same as they were on admission. The patient had very little abdominal discomfort during this time. Laparotomy was performed and a small calculus was found in the common duct. The calculus and gallbladder were removed. The pathologists' report was chronic cholecystitis and cholelithiasis. The patient's recovery was uneventful and he was discharged from the hospital in good health.

During the period from 1943 to 1952 this man considered himself entirely well. Periodic medical examinations were performed by his family doctor and no evidence of disease was ever found. Electrocardiograms were taken at the time of each examination and were always interpreted as being normal. Blood pressure usually ranged from 130/80 to 154/104. In May, 1952, the patient was struck by an automobile but was not rendered unconscious. He was taken to a hospital where the house officer observed that the patient had a drooped left eyelid, a finding the patient had been unaware of heretofore. No other abnormalities were noted. He was seen a few days later by an ophthalmologist who found the extraocular movements to be intact. One month later the patient began to note difficulty in swallowing. Food would lodge in his throat and even water was regurgitated. He was seen at this time by a neurologist who noted nasal speech and easy fatiguability, particularly of the extraocular muscles and the muscles of mastication. A test dose of prostigmin® resulted in dramatic subsidence of symptoms. A diagnosis of myasthenia gravis was made on this basis and the patient was given prostigmin 15 mg. every three hours, ephedrine sulfate 25 mg. every six hours and potassium citrate 4 gm. three times a day. Marked improvement was noted, but drooping of the left eyelid and some fatigue associated with eating and swallowing continued to be troublesome.

In spite of the patient's advanced age he was very active, routinely working late into the night in his real estate office. At 4:00 A.M. on January 9, 1956, as he was leaving his office, he suddenly had severe pain in his jaw, followed shortly thereafter by retrosternal distress and epigastric pain. He was brought immediately to Barnes Hospital. While enroute to the hospital he began to have Cheyne-Stokes respirations, and his blood pressure dropped from 170/90 to 90/60.

Physical examination revealed the blood pressure to be 85/0 and the pulse, 120. He had Cheyne-Stokes respirations. The temperature was 35.8°C. The patient was cold, clammy and

cyanotic. He appeared somewhat lethargic but was well oriented and alert. He was suffering from cramping abdominal pain and was passing a considerable amount of flatus. Examination of the head, ears, nose and throat was not remarkable. There was no hypersecretion. The pupils were miotic but reacted to light. The fundi were visualized with difficulty and the optic disks appeared flat. The neck was supple, the thyroid was not felt, and the neck veins were not distended. Examination of the lungs was normal except for a few fine, crackling rales at both bases. The left border of cardiac dulness was 10 cm. to the left of the mid-sternal line and the rhythm was regular with heart sounds of good quality. Bowel sounds were hypoactive. The liver, spleen and kidneys were not felt. There was 1+ pretibial pitting edema. Neurologic examination revealed that the patient could move all of his extremities well. The deep tendon reflexes were generally hypoactive but equal. No pathologic toe signs were noted. The cranial nerves all functioned well. Rectal examination was not performed.

The patient was immediately given 5 per cent glucose in water containing l-nor-epinephrine intravenously. The blood pressure rose to a level of 160/60. A capillary hematocrit was 50 per cent. An electrocardiogram revealed a rate of 136 and depression of the S-T segment in standard lead 1, V_7 and V_8. The T wave in V_8 was diphasic. The record was interpreted as showing sinus tachycardia with associated changes and full auriculoventricular conduction. There was marked clockwise rotation. Shortly after admission the patient was given 1 cc. of a 1:2,000 solution of prostigmin intramuscularly. This dose was repeated in two hours. He then became very restless and complained of being unable to breathe. His respiratory rate was 40 per minute. His pupils became dilated. Breath sounds were normal bilaterally. Five minutes later he suddenly became comatose gasping slowly for breath. Cyanosis deepened and the heart rate slowed. Heart sounds were described as being poor. The patient was given ½ cc. of 1:2,000 solution of prostigmin intravenously and showed marked improvement. Blood pressure rose to 130 systolic. Heart tones improved and the rate became faster. Respiratory rate at this time was 20 per minute. The peripheral pulses were strong and equal bilaterally, with the exception of the carotid pulses which were difficult to feel. However, it was thought by one observer that the right carotid pulse was probably absent and the left greatly diminished. For approximately a half hour after the intravenous administration of prostigmin the patient's condition remained unchanged. At this time, however, the intravenous solution containing nor-epinephrine had to be discontinued. Blood pressure soon fell to shock levels. The patient had a tonic seizure, became deeply cyanotic and his heart stopped beating. He continued to breathe slowly for a minute after his heart sounds were no longer audible. An attempt was made to give another dose of prostigmin intravenously, with no effect. The patient died five hours after admission to the hospital.

CLINICAL DISCUSSION

DR. CARL V. MOORE: The episode of jaundice in association with obstruction of the common duct probably does not have too much to do with the patient's subsequent course. We have then only two problems with which to concern ourselves. First, the myasthenia gravis, and second, the nature of the terminal episode. We are privileged in having Dr. Clark Millikan, head of one of the sections in Neurology at the Mayo Clinic visiting with us. I am going to vary the usual procedure of these Conferences by asking Dr. Millikan to discuss myasthenia gravis in general and in relation to this patient.

DR. CLARK H. MILLIKAN: The events of the last five hours of this patient's life were not those ordinarily associated with myasthenia gravis. The history relates that sudden pain occurred in the patient's jaw followed by substernal distress. The sudden catastrophic onset of such events at almost any age makes one think first of trouble in the vascular system. The pain in the jaw is perhaps difficult to tie in with the rest of the story. The jaw is supplied by the mandibular division of the fifth cranial nerve and the fifth cranial nerve takes origin from the region of the pons. The descending root goes down as far as the third cervical segment but may extend as far as the fifth cervical segment. Reflex connections can exist in this area as well as higher up, which may in certain instances account for pain in the jaw. Why some of these patients really have the pain is a matter for speculation. This patient is reminiscent of one observed a few weeks ago in our own institution. The latter was a man in whom sudden pain in the back of the neck and head, and difficulty in swallowing developed. Within a few minutes he had pain in the back

between the shoulder blades. There was shortness of breath. He was given narcotics elsewhere and permitted to recover partially from the effects of the medication during the course of the next four days. He was seen by us in consultation on the seventh day of his illness, at which time the only abnormal physical finding was weakness of the tongue. Later it was discovered that there was atrophy and weakness of the left side of the tongue as well as weakness of the right side of the tongue. The diagnosis of a dissecting aneurysm of the aorta was made. This man was operated upon, the diagnosis established, and repair carried out within the resources of the surgeon. It is my own belief that the diagnosis of choice in the case under discussion here would be dissecting aneurysm of the aorta.

Not infrequently the neurologist becomes involved in dissection of the aorta. Not long ago thirty-seven autopsy specimens of dissecting aneurysms were reviewed and the results indicated that definite neurologic complications are frequent. For example in two patients hemiplegia developed. Following dissection which involves the carotid circulation there can be a sufficient degree of hypoxia, at least to one-half of the brain, which may cause hemiplegia. More frequently, however, there are partial neurologic deficits, similar to the one that I related in our patient. It is noted in the protocol that the right carotid was not palpable while the left carotid had limited pulsations. The patient was conscious. There were no distinctive focal neurologic signs. It was stated that he was alert, which is an encouraging sign. Later as a terminal event he had a seizure. The part played by the seizure is difficult to explain fully. Seizures are seen in all kinds of systemic disorders and I do not think that they carry any specific diagnostic importance in a situation such as this. Hemiplegia and hemianesthesia were not observed, although neurologic examination was probably very difficult because of the patient's acute illness. We do not, therefore, have evidence to indicate that there was an actual supratentorial infarction. Whether or not something will be demonstrable in the carotid artery is difficult to say. It is not easy to assess the importance of a poorly and completely palpable carotid artery. In our experience some 5 to 10 per cent of normal patients, that is, those without a history of brain or neck disorders, have differences in the palpation of the carotids. I believe that this observation is not a surprising finding.

The diagnosis of myasthenia gravis was apparently established with a fair amount of ease. It is interesting to note that there had been a car accident at the time trouble began. One hears all kinds of stories about so-called exciting events before the onset of this strange disorder. As far as I am concerned there is no relationship between the two. The first thing noted was a unilateral partial ptosis. This complaint is one of the most common initial symptoms in myasthenia gravis. It is of historical importance in the diagnosis of myasthenia gravis that the ptosis be of recent origin. One type of ptosis is of congenital origin. There was no evidence of any involvement of other functions supplied by the oculomotor nerve. Consequently the historical development of ptosis two weeks or months before an examining physician sees a patient is important. It is up to the clinician to make the diagnosis. While electromyographic studies have shown some interesting things in myasthenia gravis, the electromyogram has not taken the place of clinical appraisal. As far as I am concerned the clinical diagnosis essentially cannot be made by any laboratory test. The diagnosis is often supported by the pharmacologic demonstration of improvement in the patient's weakness following the administration of anticholinergic agents. There has been much discussion during the last three years concerning other possible tests or technics to demonstrate the existence of a defect in transmission at the myoneural junction. If the patient has demonstrable weakness in some muscle groups, prostigmin, mestinon, tensilon® or mysuran* may be administered. The drug is given, the patient observed and the effect on the weakness noted. The weakness will be definitely improved if the diagnosis is myasthenia gravis. One of the biggest problems in a neurologic practice is presented by the patient who has been said to have myasthenia gravis because of a complaint of easy fatiguability. Many of our consultations are concerned with unraveling the diagnosis of the patient who probably does not have myasthenia gravis, but who has been given prostigmin because of tiredness and easy fatiguability and has shown some improvement. If there is no demonstrable weakness, then there is no physical evidence of myasthenia gravis. If there is no weakness following the administration of curare, then there is no pharmacologic evidence of myasthenia gravis.

* The name mysuran has recently been changed to mysurgal.

Ordinarily if there is demonstrable weakness, we perform the prostigmin test first. If a patient complains primarily of easy fatiguability, one usually will not find any evidence of ptosis, weakness of swallowing, difficulty in chewing or any manifestation of weakness of muscle groups. One must then question whether or not it is possible that this is a latent case of myasthenia gravis which under certain circumstances may make itself apparent, although it was not present at the time the patient was examined. This situation is one in which the curare test can be used with definite advantage. We have not had any difficulty with this test when it is used with great care. This is highly important. One-tenth of the curarizing dose of curare is put into a syringe and diluted to 5 cc. It is injected intravenously, ½ cc. at a time. Then one waits for two minutes by the clock, rechecks certain key muscles, such as the eye rotaters, intercostals, neck and respiratory muscles, and injects another ½ cc. increment. Difficulty has arisen in cases in which we believed the patient did not actually have myasthenia gravis and therefore only half the amount in the syringe, or $\frac{1}{20}$ of the curarizing drug, was given to start with in order to save a little time. This is not wise. If one is going to use the curare test, it is important to presume that the patient has myasthenia gravis. Prostigmin must be immediately available in another syringe and with another needle in the event that something goes wrong with the one being used. By this technic, one will have no difficulty with the test. If after injecting one-tenth of the curarizing dose no weakness develops at the end of approximately twenty to twenty-five minutes, there is no clinically significant evidence that the patient has myasthenia gravis.

Myasthenia gravis may be confused with many different diseases where it is important to establish a definite differential diagnosis, such as polymyositis. Occasionally, it becomes intermingled with thyrotoxicosis and thyrotoxic myopathy. We have seen some thirty patients with myasthenia gravis and thyrotoxicosis. At times these two diseases cause great difficulty as far as the differential diagnosis is concerned. Ordinarily, however, the patient with thyrotoxic myopathy does not respond positively to an injection of prostigmin or mestinon, tensilon or other anticholingeric drugs. The patient with thyrotoxic myopathy has a normal curare test and there is no increase in that patient's sensitivity to curare. The reflexes are essentially normal in thyrotoxic myopathy. The electromyogram shows non-specific changes, if there are any changes at all. The muscle biopsy specimen may be entirely normal, even when there is massive loss of muscle substance. In our hands the rules for therapy are relatively simple. If the patient has myasthenia gravis and thyrotoxicosis, or if a patient with myopathy has thyrotoxicosis, the latter would be treated. If there is thyrotoxic myopathy, the myopathy disappears. It has been stated on the basis of a study carried out some years ago on a few patients that there is an inverse relationship between thyrotoxicosis and the degree of myasthenia gravis. That is, when the thyrotoxicosis gets better, the myasthenia becomes worse. This has not been our experience. We have not found any consistent pattern in the thirty patients studied. In certain instances the myasthenia gravis improved when the thyrotoxicosis was treated, but this was not always the case. In some instances the myasthenia antidated the thyrotoxicosis, and in others exactly the opposite was observed.

As far as the therapy of myasthenia gravis is concerned, we have no particular preference for any anticholengeric drug. Prostigmin is the drug used most often and, as you know, it is highly important that the patient understand the action of the drug since he must experiment with his own dose.

The matter of thymoma comes up repeatedly. Of course, roentgenograms of the chest and careful examination for the presence of the tumor is indicated. When a tumor is found, we advise removal, because 10 per cent of such tumors, in our experience, become malignant. However, the effect of such removal on the myasthenia gravis is definitely not encouraging. We would make no favorable statements to the patient. Thymectomy when there is no demonstrable tumor, has been evaluated in some 175 patients. Postoperatively the chances of very marked improvement of the myasthenia gravis in women under forty are approximately six of ten; in men under forty the chances are five of ten. From that point on, in older men and older women, the results are so poor that we ordinarily do not suggest that procedure.

DR. MOORE: You stated that in the curare test you put one-tenth of the curarizing dose in the syringe. Would you please define the curarizing dose.

DR. MILLIKAN: The curarizing dose is 3 mg. per 40 pounds of body weight. That turns out to

be 1 cc. per 40 pounds of body weight. For a person weighing over 160 pounds the dose is 4 cc. One-tenth the curarizing dose, or $\frac{4}{10}$ of 1 cc., is put into the syringe and diluted to 5 cc. One-half cc. increments contain approximately $\frac{1}{100}$ of the curarizing dose and this amount is essentially safe. It might be added that we do not use the curare test when the patient has clinically demonstrable evidence of weakness. In our experience that would be asking for trouble. It is used only when we wonder about latent myasthenia that cannot be detected at the moment.

DR. MOORE: Do you use ephedrine regularly when you give prostigmin?

DR. MILLIKAN: Yes, 25 mg. three to four times a day.

DR. MOORE: Why do you use ephedrine?

DR. MILLIKAN: The use of ephedrine is based on empiric reasoning. Before prostigmin was used in myasthenia, ephedrine was thought to produce fairly significant improvement in such patients. That was before my time, so I will not take any of the blame for the statement.

DR. MOORE: Why is it that all of the involvement in myasthenia gravis seems to be of the voluntary muscles. Why is the smooth muscle not equally involved?

DR. MILLIKAN: The answer to your question involves speculation concerning the pathogenesis of myasthenia gravis. For a long time it was thought that a circulating substance might be responsible for myasthenia and many people have searched for this substance. It is true that in some instances newborn infants of mothers with myasthenia have been shown to have a myasthenia-like state for a few weeks. This observation suggests the possible existence of a circulating substance the detection of which awaits the future. No one has as yet isolated such a substance. Myasthenia gravis affects, as you have implied, certain rather specific muscles and the extraocular muscles seem to be involved more frequently. Why this is so we do not know, and why smooth muscles are spared is also unknown. Rather recently we have been taking muscle biopsy specimens from patients who have had myasthenia gravis for a long time, and have found that there is a change in the muscle. Our belief is that there is possibly something fundamentally wrong with the muscle rather than with the synthesis of acetylcholine as suggested by the Cornell group, but I cannot answer the question.

DR. MOORE: Dr. Berg, one of the things that bothered the house staff when this man was admitted in the terminal episode was whether or not he may have received an overdose of prostigmin. What happens when that occurs, and can you eliminate the possibility of an overdose of prostigmin in this patient?

DR. LEONARD BERG: The pertinent effects of an overdose of prostigmin are those related to excessive parasympathetic activity, so that the principal complication about which we have to be concerned is the flooding of the tracheobronchial tree with secretions. There has long been a debate about whether or not an overdosage of prostigmine will adversely influence skeletal muscle function, so that the idea of a "cholingeric crisis" producing markedly increased myasthenic weakness has gained some attention. There were no clear-cut data in the literature until Rowland and his group at the National Institute of Health studied prostigmin infusions in a series of patients with myasthenia. It was apparent that when intravenous prostigmin was given in large doses (rates of 2 to 10 mg. per hour), an acute increase of muscular weakness would result. Patients with more severe myasthenia required larger doses at greater rates. It has therefore been clearly established that overdosage of prostigmin will increase skeletal muscle weakness.

When one is faced with the treatment of patients suffering from an overdosage of prostigmin, the care of the tracheobronchial tree requires prompt attention with atropinization, drainage, suction and tracheotomy, as necessary. So far as we know there is nothing that can be done about the adverse effect on skeletal muscle, other than assisting respiratory function with a mechanical respirator.

DR. MOORE: Dr. Smith, do you agree with Dr. Millikan that the most likely explanation for the terminal episode was that this patient had a dissecting aneurysm?

DR. JOHN SMITH: Yes, I think that is the most likely explanation of his symptoms in the absence of electrocardiographic findings. However, I would also consider myocardial infarction.

DR. MOORE: Would you discuss the possibility of myocardial infarction in more detail. In myocardial infarction epigastric distress and severe pain radiating to the jaw can develop. One can raise the blood pressure initially only to have it fall precipitously as it did in this man. Initially one can hear sounds that are of good quality and do not have a gallop or other murmurs. Some-

times, it takes a little while before the electrocardiogram shows evidences of myocardial infarction. How are you so certain about eliminating the diagnosis of myocardial infarction in this patient?

DR. SMITH: Your statements are certainly true. It would be less common, in my experience, to have a myocardial infarction present in this manner. Although negative electrocardiographic signs do not rule out myocardial infarction, the manifestations of pain, including radiation to the face, and the general progression of the disease in this case, are more typical of aortic disruption.

DR. MOORE: Dr. Massie, would you care to comment about the electrocardiograms and make any other comment about the terminal episode.

DR. EDWARD MASSIE: When I read the protocol, I thought of three possibilities: (1) dissecting aneurysm, (2) coronary thrombosis and (3) pulmonary infarction. I considered dissecting aneurysm the most likely of the three. I do believe that your statements presenting arguments in favor of the possibility of myocardial infarction are valid. Therefore, one has to look at the other aspects of the case to make the differentiation. This patient was admitted in shock and died in a rather short time. If a patient with acute infarction is in shock and an electrocardiogram is taken at that time, one would expect more specific changes than those seen in this patient's tracing. This electrocardiogram showed no evidence of myocardial infarction. If anything it showed marked clockwise rotation which is in favor of pulmonary complications. Also, the patient had considerable air hunger. On the basis of that observation I believed that pulmonary infarction was the second best choice. However, a recent article in Modern Concepts of Cardiovascular Disease stresses that air hunger is a prominent finding in dissecting aneurysms. I have seen air hunger begin several weeks before the acute episode. Also, jaw pain, as Dr. Smith has just stated, is not uncommon in dissecting aneurysm. In acute infarction, however, when there is jaw pain, it is usually accompanied with considerable chest pain as well. Perhaps this patient did have chest pain, but it is not stressed in the protocol. The only positive way to differentiate dissecting aneurysm from myocardial infarction is by the electrocardiogram. The electrocardiogram is normal in dissecting aneurysm unless there is dissection involving the coronary ostia. Since this patient's tracings were normal one would be swayed toward the diagnosis of dissecting aneurysm. My conclusion would be that dissecting aneurysm is the most likely diagnosis here. I am sure he had some coronary disease but no acute infarction. Pulmonary infarction is possible but unlikely.

DR. MOORE: Dr. Millikan, how do you explain the fact that this man seemed to improve so much when he was given one dose of prostigmin? Do you believe that this response implies that his need for prostigmin rose to such an extent when he had this acute accident that we erred in not giving him enough drug?

DR. MILLIKAN: I do not believe there was a serious error in not giving him enough prostigmin. Incidently, the problem of an overdosage of prostigmin is one that frightens us frequently, especially if the patient is acutely ill with chronic myasthenia. It may be very important to stop all medications and put the patient in a respirator to permit the effects of prostigmin to wear off. One may also try some additional prostigmin to see whether or not the patient improves, as this man did. I do not believe that this patient's terminal event was materially influenced by inadequate therapy of myasthenia.

DR. MOORE: The impression of the house staff when this patient was admitted was that he had myocardial infarction but during the few hours that he was in the hospital it was definitely changed to one of dissecting aneurysm. My own thought is that one would have to put dissecting aneurysm as the first choice by a narrow margin. I do not see how one could possibly be surprised if, instead of a dissecting aneurysm, a myocardial infarct was demonstrated.

PATHOLOGIC DISCUSSION

DR. JAMES C. HARKIN: The principal anatomic finding was a dissecting aneurysm of the aorta. The lumen of the aorta and that created by the dissection communicated at a transverse rent in the arch of the aorta 6 cm. distal to the aortic valve. Proximally, the dissection extended into the root of the aorta with hemorrhage into the epicardium and atrium with hemopericardium (250 cc.). The orifices of the major branches from the aortic arch were spared. The diagram illustrates how throughout the remainder of the aorta, the medial dissection was not completely circumferential, but spared a band anteriorly. (Fig. 1.) Thus the renal and mesenteric arteries and the celiac axis arose from

that part of the aorta not directly involved by the dissection. Inferiorly, no second communication with the aortic lumen occurred, there being a blind end in the proximal segment of each iliac artery.

Microscopically, the aortic wall was strikingly

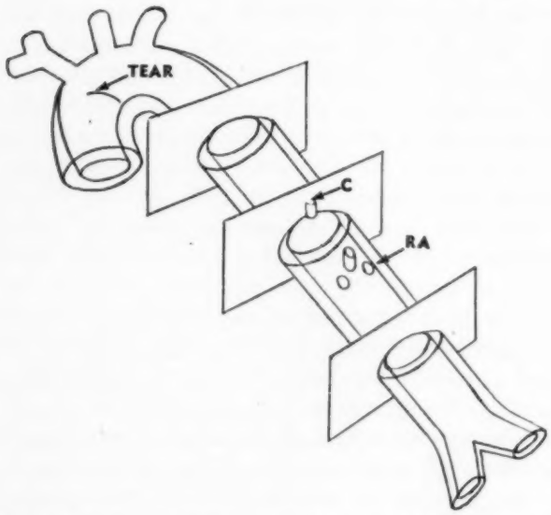

FIG. 1. Diagram of the aorta, from its anterior aspect. At the root of the aorta, the lumen of the dissection can be seen surrounding the aorta. Note that the dissection does not extend up the vessels arising in the arch. The planes taken through the aorta show the appearance of the cross section at various levels. Note how the renal artery (RA) and the celiac axis (C) lie in that part of the aorta not the seat of medial rupture.

depleted of elastic fibers. In addition, the relatively acellular media was metachromatic when stained with toluidine blue. Small medial cysts were not a prominent feature. The systemic arteries were the seat of severe arteriosclerosis.

None of the morphologic alterations frequently associated with myasthenia gravis were found. Thymic tissue was not identified.

Other anatomic diagnoses included a saccular arteriosclerotic aneurysm of the left iliac artery, moderate arteriolar nephrosclerosis, cardiac hypertrophy and dilatation (450 gm.), an old infarct of the superior pole of the spleen, a solitary calculus in the left renal pelvis, minimal anthracosilicosis of the hilar lymph nodes, and a cicatrix at the bed of the surgically absent gallbladder.

Although the etiology of dissecting aneurysm of the aorta remains unknown, two groups of observations have been made: (1) studies on the disease as it occurs in humans, particularly with respect to its association with other conditions and (2) studies on the experimental production of medial dissection.

At autopsy, particularly in specimens removed from older patients, it is possible to separate readily the aorta along a natural line of cleavage in the outer part of the media at approximately the same site where dissecting aneurysms occur. Clinically, hypertension is commonly associated with medial dissection of the aorta, and less frequently the tears occur during the late part of pregnancy. The most interesting association of lesions is in Marfan's syndrome where not only is there dissection of the aorta, but also other alterations of mesenchymal tissues with loosening of tendinous and ligamentous insertions, arachnodactyly and dislocation of the lens.

Early attempts at the experimental production of aortic dissecting aneurysm centered on mechanical damage to the aorta and the vasa vasorum. It is difficult to produce necrosis of the media in such a fashion unless a rather severe degree of damage to the aorta is sustained, for example by cautery of the adventitia. Certainly alterations of the vasa vasorum are present in most cases of dissecting aneurysm in humans, but from the experimental data it would seem possible to explain these changes as those that follow rather than precede the initial insult to the aorta.

By methods intended to alter or interfere with the metabolic processes of tissues, it has been possible to produce aortic dissections. Three groups of changes of these types have been produced: (1) by feeding rats seeds of the sweet pea Lathyrus odoratus,[1–3] (2) by cortisone administration in hamsters[4] and (3) by feeding poultry under special commercial conditions.[1] The condition most thoroughly studied is the one of lathyrism in rats.

Before considering this condition it might be worth while to make an aside remark about lathyrism in humans, which is not related to the disease produced in rats by the sweet pea L.

[1] STRONG, F. M. Lathyrism and odoratism. *Nutrition Rev.*, 14: 65–67, 1956.

[2] BEAN, W. B. and PONSETI, I. V. Dissecting aneurysm produced by diet. *Circulation*, 12: 185–192, 1955.

[3] WAWZONEK, S., PONSETI, I. V., SHEPARD, R. S. and WIEDENMANN, L. G. Epiphyseal plate lesions, degenerative arthritis and dissecting aneurysm of the aorta produced by aminonitriles. *Science*, 121: 63, 1955.

[4] STEFFEE, C. H. and SNELL, K. C. Dissecting aortic aneurysm in hamsters treated with cortisone acetate. *Proc. Soc. Exper. Biol. & Med.*, 90: 712–714, 1955.

odoratus. The specific chemical responsible for the disease in rats, beta-amino propionitrile is not present in the species of peas responsible for the human disease. The human disease of lathyrism is a neurologic condition usually observed in the Middle East during times when enormous quantities of pea seeds are consumed. The human disease is characterized by weakness, parasthesia, spasticity and other signs of the same type.

On the other hand, lathyrism in experimental animals is a disease of mesenchymal tissues. There is aortic medial necrosis and dissecting aneurysm formation. In addition, there is loosening of ligamentous and tendinous insertions, slipping of the epiphyseal plates, kyphosis, scoliosis and hernia formation. It is of particular interest to note how this condition mimics certain human diseases of unknown etiology, and especially parallels Marfan's syndrome. The dissecting aneurysm produced in experimental lathyrism seems morphologically identical with the one in humans, insofar as can be determined. The earliest lesion in the aorta has not yet been unequivocally determined. It would appear that it is either destruction of the elastic tissue or perhaps an even earlier, as yet obscure, alteration in the ground substance. Whatever the initial lesion is, the greatest significance of these investigations seems to lie in the elucidation of the pathologic mechanisms of those obscure diseases of mesenchymal tissues which may prove to be caused by functional impairment of basic metabolic pathways.

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Case Reports

Idiopathic Hypoparathyroidism and Addison's Disease*

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THE concurrence of adrenal cortical insufficiency and parathyroid deficiency in the same patient is a rare phenomenon. Leonard[1] in 1946 presented the only well documented report in which autopsy confirmed the presence of these diseases in a patient who had been carefully and completely studied prior to death. Leifer and Hollander[2] in 1953 and Papadatos and Klein[3] in 1954 reported the clinical history and detailed laboratory studies supporting the presence of both of these glandular deficiencies in two patients who were clinically improved on an appropriate therapeutic regimen. However, necropsy was not performed in these instances. Previously, Sutphin, Albright and McCune,[4] and Talbot, Butler and MacLachlan[5] had reported similar cases. However, as Leifer and Hollander[2] pointed out, although the presence of Addison's disease had been proved in Talbot's patient, the authors did not present data which supported the clinical impression of hypoparathyroidism. The patient reported by Sutphin et al. had hypocalcemia and tetany without hyperphosphatemia. The tentative diagnosis of Addison's disease in this patient was based upon the presence of increased melanin pigmentation, hypotension and weight loss.

In the case report herein presented both the clinical and laboratory data clearly establish that the patient had marked parathyroid and adrenocortical insufficiency. The autopsy data confirmed the clinical diagnosis of both hypoadrenocorticism and hypoparathyroidism.

CASE REPORT

Patient J. L., a twenty-nine year old single white Syrian woman, was admitted to the Maimonides Hospital in Brooklyn on July 10, 1949, because of disorientation and dysarthria of two hours' duration. Since the age of ten the patient had been having spells of unconsciousness associated with stiffening of the arms and legs, jerking movements of both hands and gritting of the teeth. Occasionally these "fits" were associated with falling to the floor and with incontinence of feces and urine. These attacks usually lasted for about one minute and were not followed by somnolence. There was no regularity about the appearance of the attacks: At times they appeared two or three times a day and at times they disappeared for three to four months. During the few months prior to admission to the hospital, the frequency of the attacks varied from approximately twice a day to twice a week. Shortly before hospitalization the attacks were more frequent in the morning prior to breakfast. There also appeared to be an increased incidence of attacks at the time of menstruation.

Five years prior to hospitalization she had been seen by another physician, and at this time the neurologic examination revealed no abnormalities. The blood pressure was 118/90. The serum calcium concentration was 8.8 mg. per cent and the serum phosphorus was 4.0 mg. per cent. The electroencephalogram was reported to be "abnormal but not diagnostic of a convulsive disorder." Neither dilantin® nor phenobarbital seemed to decrease the frequency or severity of these convulsive attacks. No history of injury at birth or subsequent head trauma was noted. No other member of her family was known to have had any convulsive disorder or migraine.

Two years prior to this admission to the hospital, progressive bronzing of the skin was noted. The patient gradually lost 25 pounds; no anorexia, nausea, vomiting or diarrhea occurred. Six months later muscle weakness was noted and gradually became worse. Her family physician suspected that adrenal insufficiency was the cause of some of the symptoms. A few injections of adrenal cortical extract were given

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without much symptomatic improvement. On the morning that she was admitted to the hospital, she was found in bed in a confused state.

The menarche had occurred at thirteen years of age. For the first year thereafter the menstrual periods were irregular. For the next ten years the menstrual periods occurred at regular intervals of four weeks, but during the past five years the menses occurred at thirty to ninety day intervals. There was no history of exposure to tuberculosis. The medical history was noteworthy only in that at age eleven she had had a giant cell tumor of the right tibia curetted. This lesion recurred during the following year and a second curettage was performed. No further recurrence was demonstrable by x-ray study.

The physical examination revealed a bronzed, asthenic young woman who appeared both acutely and chronically ill. The rectal temperature was 104°F., the pulse rate 120 per minute, the respiratory rate 22 per minute and the blood pressure 65/40. The patient made apparently purposeless movements of her fingers which at times resembled the carpal spasm of tetany. However, neither Chvostek's nor Trousseau's signs could be elicited. The skin was dry and hot. No cataract was noted in either lens. Irregular areas of brownish pigmentation were present on her face and on the scars on her body. An area of vitiligo was also present on her neck. The gingivae were markedly hypertrophied and the buccal mucosa contained brown pigment. The palmar creases of the hands were deeply pigmented. The nails were normal. The teeth were small and transverse ridging of the anterior incisors was noted. Slight blurring of the nasal border of the left optic disc was noted. There was no opacity of the lens or cornea. The axillary and pubic hair were normal in both quantity and distribution. No abnormal findings were noted in the chest, abdomen or pelvic regions. The neurologic examination revealed no abnormalities other than the purposeless movements already mentioned.

The urine contained no glucose, albumin or abnormal cells. The maximum specific gravity was 1.023. The excretion of phenolsulfonphthalein during a two-hour period was 70 per cent. The urea clearance was 105 and later 72 per cent of normal. The blood urea nitrogen concentration ranged between 9 and 14 mg. per cent on numerous occasions. The hemoglobin concentration varied from 10 to 13 gm. per cent and the red blood cell count from 3.5 to 4.5 million per cu. mm. The white blood cell count, which was 39,000 with 94 per cent neurophils when the patient was admitted to the hospital, decreased to normal within a few days. The corrected sedimentation rate (Wintrobe method) ranged between 30 and 43 mm. per hour throughout the hospital stay. The blood sugar concentration was 50 mg. per cent (Somogyi precipitation method), the serum chloride concentration was 99 mEq./L., the serum CO_2 was 22 mEq./L. Following the initial therapy, the serum sodium concentration was 134 mEq./L. and the serum potassium concentration was 6.3 mEq./L. The cerebrospinal fluid was under a pressure of 120 mm. of saline solution. There were two mononuclear cells cu. mm. The spinal fluid sugar was 40 mg. per cent, the protein was 36 mg. per cent, the chloride was 129.5 mEq./L. and the calcium was 2.4 mg. per cent. Both the colloidal gold curve and the Wassermann test of the spinal fluid gave normal results.

Upon admission to the hospital a tentative diagnosis of acute adrenal insufficiency was made. The patient was, therefore, given intravenous infusions of glucose, saline solution and adrenal cortical extracts. An injection of 20 mg. of desoxycorticosterone acetate (DOCA®) was administered intramuscularly. After twenty-four hours the temperature decreased to 102°F. No cause for the fever was apparent; nevertheless 1.2 million units of procaine penicillin per day were injected intramuscularly. Within three days the fever had disappeared and did not recur during the hospital stay.

METABOLIC STUDIES

Adrenocortical Status. When the patient was no longer acutely ill, studies were made to confirm the clinical diagnosis of adrenal insufficiency. Since, as will be pointed out subsequently, the patient also revealed clinical evidence of hypoparathyroidism, some of the tests of adrenocortical function were made during the period of hypocalcemia and repeated during the period when the serum calcium concentration remained normal. Thus the effect of hypocalcemia upon adrenocortical function could be observed. The data are presented in Table 1.

It is apparent from these data that the Kepler-Power water test gave results suggestive of adrenal insufficiency. (Night urinary volume was greater than maximum hourly day volume and the "A value" was less than 25 in two of three tests.) The daily urinary excretion of 17-ketosteroids was also below normal levels in three of four assays. After induced hypoglycemia the eosinophils in the peripheral blood did not decrease by 50 per cent. After injection of adrenalin® the fall in eosinophil count was greater than 50 per cent in two of three tests. The response of the blood glucose levels revealed insulin hypersensitivity (the blood glucose dropped to 8 mg. per cent) but in two of the three tests the blood glucose returned to preinjection levels. In the third test the blood glucose level failed to reach the initial concentration. These results would indicate that there was moderate but not complete decrease of adrenocortical influence upon carbohydrate metabolism. No

TABLE 1

Test of Adrenocortical Function	Period of Hypocalcemia	Period of Normal Calcemia
Kepler-Power water test:		
Part I	290 cc. urine at night; 75 cc. max. hourly excretion during day	540 cc. urine at night; 145 cc. max. hourly excretion during day
Part II ("A value")	20 and 26	22
Urinary excretion of 17-ketosteroids	6.1, 2.7, 2.3 mg. per day	2.9 mg. per day
Eosinophil decrease after:		
I. 0.5 ml. 1/1,000 adrenalin, subcutaneously	From 114 to 26 per cu. mm. From 90 to 30 per cu. mm.	From 84 to 78 per cu. mm.
II. Hypoglycemia due to intravenously injected insulin	From 48 to 36 per cu. mm. From 72 to 51 per cu. mm.	From 96 to 96 per cu. mm.
Glucose response to intravenously injected insulin:		
I. 0.05 units/kg	Fasting 84 mg. % Lowest, 30 mg. % 1–2 hr. level, 70–80 mg. %	Fasting, 55 mg. % Lowest, 25 mg. % 1–2 hr. level, 50–75 mg. %
II. 0.1 units/kg	Fasting, 92 mg. % Lowest, 8 mg. % 1–2 hr. level, 50–62 mg. %	....

apparent difference was noted in adrenocortical function when the hypocalcemic state was compared with the period of normal serum calcium concentration.

The patient was apparently kept in good clinical condition by daily intramuscular injection of 5 mg. DOCA and by daily ingestion of 6 gm. of enteric-coated salt in addition to a regular diet. Figure 1 demonstrates that upon this therapeutic regimen a systolic blood pressure of 80 to 100 mm. Hg and a diastolic pressure of 50 to 70 was maintained. Her weight fluctuated between 106 and 114 pounds. The serum concentration of sodium and potassium remained within normal limits.

X-ray studies revealed a small heart shadow; no evidence of pulmonary tuberculosis was present. No calcification was noted in the adrenal area. The tuberculin skin patch test gave a positive result.

Parathyroid Status. The initial concentration of the serum calcium was 7 mg. per cent, of the serum phosphorus 5.7 mg. per cent. Repeated studies of these serum electrolytes revealed a range of serum calcium from 5.2 to 7.7 mg. per cent and of serum phosphorus from 4.3 to 7.5 mg. per cent. The urine failed to reveal any calcium when tested with the Sulkowitch reagent. The serum proteins were normal. Roentgen examination of the skull revealed non-specific rarefaction of the alveolar processes and increased density of the roots of the teeth. No calcification of the basal ganglia was noted. The sella turcica was normal. X-ray studies of the hands and long bones of the extremities revealed no abnormalities.

During a preliminary period of two weeks on a regular diet persistent hypocalcemia and hyperphosphatemia were noted. The patient was then placed on a diet containing 600 mg. of calcium and 1500 mg. of phosphorus per day. In addition, 2 gm. and later 4 gm. of calcium gluconate were given each day. For one week, one of the authors, a woman of approximately the same size, weight and age as the patient, ingested the same diet and doses of calcium gluconate. As will be noted in Figure 2, while on this regimen the patient's serum calcium level remained low and serum phosphorus level remained high. The daily urinary excretion of calcium by the patient was approximately 20 to 30 mg. as compared with an excretion of 150 to 200 mg. by the normal control subject. The daily urinary excretion of phosphorus by the patient (despite the hyperphosphatemia) was only approxi-

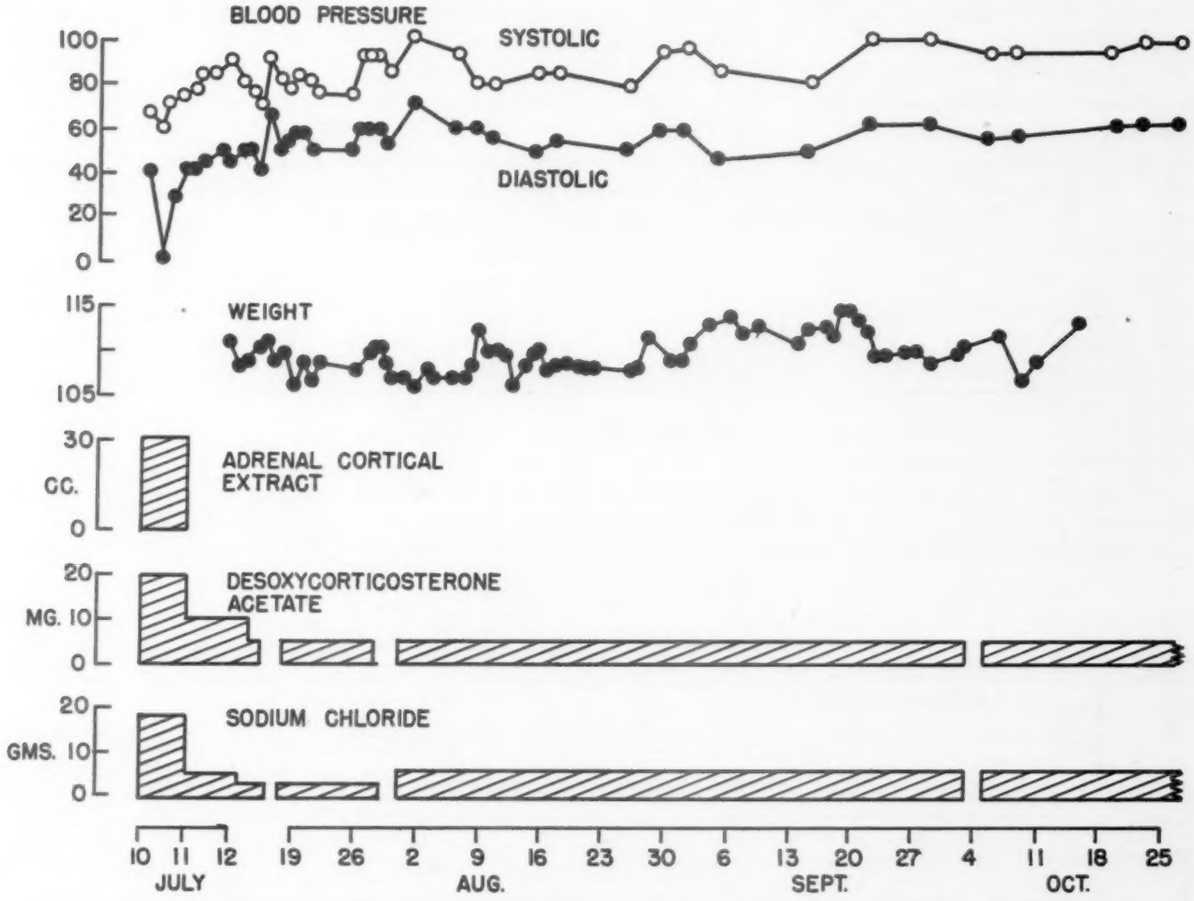

FIG. 1. The effect of therapy for adrenocortical insufficiency upon blood pressure and body weight.

mately 300 mg. per day as compared with an excretion of approximately 600 mg. per day by the normal control subject. This demonstrated that the patient had definite hypocalciuria and hypophosphaturia, despite the hyperphosphatemia.

The patient then received intramuscular injections of parathyroid hormone in order to determine whether the kidney tubules could respond to parathormone. At first she received 100 units per day, then 250 units per day and later 500 units per day; no definite increase in phosphaturia, calciuria, rise in level of serum calcium or drop in serum phosphate level occurred. However, when 1,000 units of parathormone were injected daily, there was a definite drop in the serum phosphate concentration and a rise in both serum calcium concentration and in the phosphaturia. The calciuria increased only slightly. Upon cessation of the parathormone injection the serum and urinary concentrations of both electrolytes returned to pretreatment levels. Dihydrotachysterol was then administered orally in doses of about 4 mg. per day. During administration of this therapy a definite rise of the serum calcium level was noted with but a slight drop of the serum phosphate level. The urinary excretion of calcium was increased to about ten times the pretreatment level; the phosphaturia increased minimally.

The electrocardiogram during the hypocalcemic and hyperkalemic period showed prolonged Q-T interval and high voltage T waves in all the leads. During the period when these serum electrolytes were normal, the T waves were a little lower than previously and the Q-T interval was within normal limits.

Thyroid Status. The basal metabolic rate was minus 16 and later minus 19 per cent. The serum cholesterol was 266 and 245 mg. per cent. The serum protein bound iodine was 2.8, 4.0, 1.5 and 2.0 gamma per cent. (The normal range in this laboratory is 3.0 to 7.0 gamma per cent.)

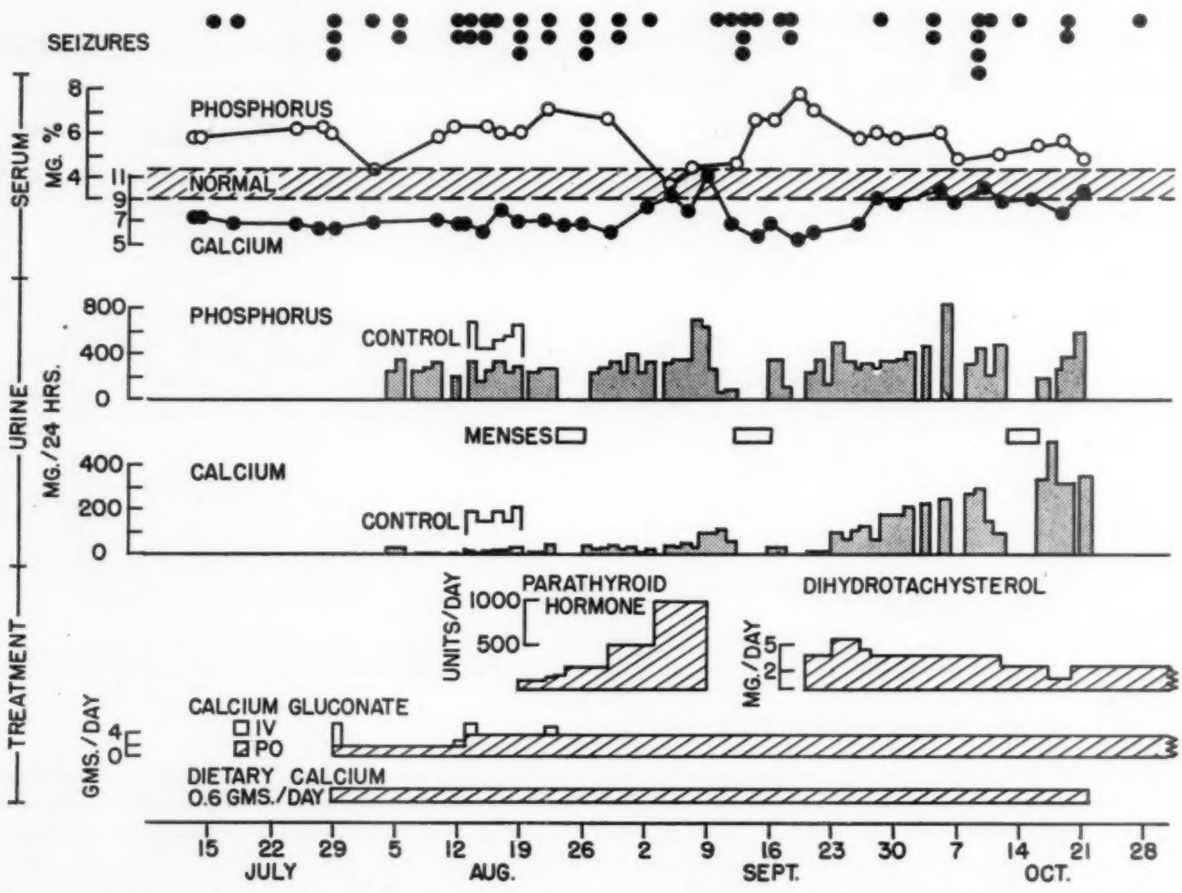

FIG. 2. The effect of therapy for parathyroid insufficiency upon frequency of epileptic attacks, level of serum calcium and phosphorus, and urinary excretion of calcium and phosphorus.

The uptake of radioactive iodine by the thyroid gland was 30 per cent in twenty-four hours. (The normal range in the laboratory at that time was 10 to 40 per cent.) Thus the data suggested a slight decrease in thyroid function.

Cerebral Status. The patient had brief episodes of mental confusion, unresponsiveness and rhythmic movements of the jaws, as well as two major convulsions during this period in the hospital. The major convulsions were preceded by an aura of impending disaster and were characterized by tonic movements of the extremities. The seizures terminated with a brief coughing spasm. The patient never remembered any of these episodes. The association between the convulsions and the blood levels of both sugar and calcium was studied. Strangely enough, convulsions did not occur during the three periods of hypoglycemia induced by the intravenous injection of insulin. At one time a blood sugar of 8 mg. per cent was reported without any convulsive seizure having taken place. Nor did hypocalcemia appear to be a major factor in the convulsive tendency, since the seizures were only slightly less frequent during the period of normal serum calcium levels. The convulsions did seem to be more frequent just before and during the menstrual periods. Carpal spasm could be provoked during the hypocalcemic period by hyperventilation. During maintenance therapy of 1.25 mg. of dihydrotachysterol and calcium gluconate, the patient continued to have normal serum calcium levels. However, during one menstrual period, which was associated with an increase in the frequency of the convulsions, a rapid drop in the serum calcium level to 6.1 mg. per cent was noted. The serum calcium level rose to 10.6 mg. per cent without change in the therapy when the menstrual period was over.

An electroencephalogram taken during the hypocalcemic period showed a predominant 5 to

7 cycle/second discharge. Hyperventilation increased the slow activity discharges especially in the anterior areas. An electroencephalogram taken during the period of normal serum calcium concentration (while ingesting dihydrotachysterol) revealed an irregular pattern consisting chiefly of low voltage activity, irregular alpha frequencies and occasional moderate voltage 5 to 6 cycle per second potentials. Hyperventilation resulted in occasional high voltage 3 to 4 cycle/second discharges especially in the frontal and parietal leads. The last test was interpreted as indicating a moderate diffuse abnormality of somewhat lesser degree than that noted in the first test.

Hepatic Status. Approximately two months after admission to the hospital, the edge of the liver was palpated about one fingerbreadth below the costal margin. At this time the patient did not complain of abdominal discomfort, the cephalin flocculation test was 2 plus and the thymol turbidity test was 10 units. No retention of bromsulphalein occurred fifty minutes after injection of the dye. One month later the liver edge was palpated three fingerbreadths below the costal margin and the cephalin flocculation test was 4 plus, the thymol turbidity 12 units. The patient did not complain of abdominal discomfort.

ENDOCRINE CLINIC FOLLOW-UP

The patient was discharged to the clinic for follow-up (which ultimately extended from October 1949 to July 1950) and further therapy. She received the following medication per day: 5 mg. DOCA, 6 gm. salt, 4 gm. calcium gluconate, 2.5 mg. dihydrotachysterol and 0.1 gm. mesantoin. After a few weeks four pellets of DOCA (each containing 125 mg.) were implanted subcutaneously and intramuscular injection of DOCA was discontinued.

On this regimen the patient felt well and had no weak spells, nausea or diarrhea. Her weight varied between 113 and 117 pounds, and the systolic blood pressure remained about 100 mm. Hg. The patient experienced about twenty convulsive seizures from October to April. During this time the serum calcium level ranged between 8.9 and 10.3 mg. per cent. The liver edge was constantly felt at 2 to 3 fingerbreadths below the costal margin, and the cephalin flocculation test remained 4 plus.

During the latter part of June and the first week in July mild anorexia, weakness, diarrhea and weight loss were noted. The blood pressure fluctuated between 80/65 and 95/55. The patient was re-admitted to the hospital for more intensive adrenocortical hormone replacement therapy and re-implantation of DOCA pellets.

SECOND HOSPITALIZATION

Physical examination made during the second hospital stay (July 7, 1950 to July 22, 1950) revealed that the patient was comfortable and not dehydrated. She weighed 106 pounds, the blood pressure was 90/70. No physical abnormalities were noted other than those previously described. The urine was normal. The hemoglobin was 10 gm. per 100 cc. and the hematocrit was 26 per cent. The white blood cell count gave normal results. The fasting blood sugar level was 60 mg. per cent, the blood urea nitrogen was 15 mg. per cent, the serum albumin and globulin were each 3.3 gm. per cent. The serum calcium level was 8.6 mg. per cent and the serum phosphorus 6.2 mg. per cent. The serum sodium was 148 mEq./L., the serum potassium was 3.4 mEq./L., the serum chloride was 111 mEq./L. and the serum CO_2 was 27 mEq./L. The cephalin flocculation test was 3 plus and the thymol turbidity was 12.4 units. The serum cholesterol was 186 mg. of which 26 per cent was in the free form.

Injections of 5 mg. of DOCA per day were administered in addition to the ingestion of 6 gm. of salt and a regular diet. Within three days the anorexia and diarrhea had ceased and the patient felt considerably improved. However, on the ninth day of hospitalization a low grade fever developed and during the following week the temperature gradually rose from 100° to 104°F. No symptoms or signs were present which could explain the fever. All other pertinent laboratory tests were also non-contributory; they included many white blood cell counts, routine urinalyses, cultures of the urine, stool and blood, serum agglutinations for typhoid, paratyphoid and shigella bacteria, cold agglutination, heterophil agglutination, search for malaria parasites, and roentgen examination of the lung. Chemical determinations of the serum sodium, calcium and blood sugar all gave normal results. However, a decrease in the serum potassium to 2.3 mEq./L. was noted. When this was noted potassium chloride was prescribed, 1 gm. four times a day. The anemia gradually increased, the hemoglobin dropped from 10 to

8 gm. and the red blood count from 3.0 to 2.7 million per cu. mm. Two transfusions of 500 cc. of blood each were given. After these transfusions the patient's temperature rose to 104°F.; for the last two days of her life the temperature continued to rise to 104°F. each evening.

During the twenty-four hours prior to her death the patient began to have intermittent convulsions. These seizures were associated with apparent clinical cardiac standstill; therefore, a direct-writing electrocardiograph machine was attached to the patient. Attacks of ventricular extrasystoles, ventricular tachycardia and even short periods of ventricular fibrillation were observed. Parenteral administration of calcium gluconate, sodium amytal,® potassium chloride, quinidine and pronestyl® was instituted. This resulted in return of the heart rate to regular sinus rhythm. However, five hours later no pulse could be found, breathing was shallow, and within ten minutes she was dead.

Postmortem Examination. Permission for autopsy examination was restricted and the brain could not be studied. The skin of the patient was dusky and bronzed. The nails were normal. A few fine adhesions were noted on the right upper lobe of the lung to the pleura. There was a small patch of indurated pleura. The heart weighed 245 gm., and the pericardial cavity contained 25 cc. of clear straw-colored fluid. The liver extended 3 to 4 cm. below the costal margin. It weighed 1,525 gm. and was dusky red-brown. Some accentuation of the lobular architecture was noted. The spleen, which weighed 280 gm., appeared normal except for the increase in size. The kidneys were normal. The uterus, including the cervix, measured 8 by 5 by 2 cm. Small subserous myomas were noted. There was a small cyst on the left ovary. The adrenal glands were markedly decreased in size. The right measured 5 by 1.3 by 0.3 cm., the left 6.8 by 1.2 by 0.4 cm. They were both gray with an occasional yellow fleck. The normal corticomedullary ratio of the adrenal was reversed in this case, the medulla being larger than the cortex. Eight discrete small yellow nodules were dissected from the thyroid gland but these did not reveal evidence of parathyroid tissue. The thyroid was normal in size and consistency.

The adrenal cortices were no longer recognizable, being replaced by dense hyaline connective tissue. In many areas this tissue was acellular. In other areas scattered lymphoid cells or small accumulations of lymphoid cells were noted. The medulla revealed slight fibrosis.

The sections taken originally revealed no parathyroid glands. Subsequently, the perithyroid and paratracheal soft tissues were sectioned in entirety but no recognizable parathyroid gland tissue was found. In the thyroid small acini were noted, either empty or containing a small quantity of colloid. Increased intra- and perilobar fibrosis was present, with accumulations of lymphoid cells and lymphoid follicles. The entire thyroid gland was sectioned without revealing any parathyroid tissue. The ovary contained microfollicular cysts. Examination of the liver revealed a few scattered periportal fields showing granulation and increased connective tissue with lymphoid cells. Bile duct proliferation also was noted in a number of these fields. The lobular architecture was not disturbed. The liver cells revealed no essential change. The spleen showed only sinus congestion. In the heart there was fragmentation of fibers; no other essential changes were noted. The lungs showed edema and congestion. Foci of fibrosis were present. Heart failure cells were noted. No essential changes were found in the gastrointestinal tract, striated muscle, spinal cord, breast, lymph nodes and pancreas.

Major final diagnosis: (1) atrophy of adrenal glands, (Addison's disease, clinical); (2) absence of parathyroid glands (hypoparathyroidism, clinical); (3) idiopathic epilepsy, clinical; (4) pulmonary edema and congestion; and (5) an hepatic condition similar to that seen in postinfectious hepatitis.

COMMENTS

Pituitary-Parathyroid Interrelationship. It has been proved beyond doubt that the pituitary gland has trophic influences upon the adrenal cortex, the thyroid gland and the gonads. However, the influence of the pituitary hormones upon the parathyroid glands remains the subject of conflicting reports. Albright and Reifenstein[6] stated that one does not find clinical evidence of hypoparathyroidism in hypopituitarism. Nevertheless, there are data which do suggest that there might be some indirect relationship between these two endocrine glands. Houssay[7] reported that in hypophysectomized dogs some atrophy of the parathyroid glands occurred which was not accompanied by any fall in the concentration of serum calcium. This observation was corroborated by the clinical

findings of Castleman and Hertz,[8] Sheehan and Summers,[9] and Rupp and Paschkis.[10] These three groups of investigators reported some atrophy of the parathyroid glands in patients with hypopituitarism. Of the parathyroid glands of the panhypopituitary patients of Castleman and Hertz,[8] 90 per cent was composed of fat cells. However, since hypoparathyroidism was not suspected during the patients' life, no determinations of the serum calcium or phosphorus concentrations were made. Sheehan and Summers[9] reported that detailed study of the parathyroid glands of their patients who had died of hypopituitarism revealed that the oxyphil cells were either scarce or absent. In addition, they observed that the serum calcium concentrations of these patients were minimally lowered and the plasma phosphate concentrations were minimally elevated; but these variations from the normal were not significant. Rupp and Paschkis[10] reported one well documented case of a patient who had hypopituitarism with marked atrophy of the pituitary, thyroid, adrenal glands and gonads. This patient developed hypocalemic tetany, unassociated with hyperphosphatemia, four days prior to death. No parathyroid glands were found despite a careful search at autopsy. These investigators also reported that in five other cases of panhypopituitarism the levels of serum calcium and phosphate were within normal limits. These authors concluded that the decrease in the number of parathyroid cells which follows hypophysectomy or pituitary destruction probably reflects the decrease in general body weight and activity rather than the loss of a specific parathyrotrophic hormone.

Tornblom[11] made a most extensive study of the interrelation of the pituitary gland, the parathyroid gland and the metabolism of calcium and phosphate. He reported three significant findings: (1) When normal animals were fed a diet low in calcium content and high in phosphate content the parathyroid glands were overactive and the serum calcium level decreased while the serum phosphate level rose. However, when hypophysectomised animals were fed the same diet the parathyroid glands were not overactive despite the low serum calcium concentration, and the serum phosphate level did not rise. (2) Intravenous injection of phosphate solution into normal animals stimulated the endogenous production of parathormone. (3) Whereas parathyroidectomized animals exhibited the typical high serum phosphate concentration and low serum calcium concentration, hypophysectomized-parathyroidectomized animals failed to show an elevated serum phosphate level. Tornblom concluded that the pituitary hormones induced a rise in serum phosphate and thus indirectly stimulated the parathyroid glands. Thus in pituitary failure the serum phosphate did not rise and, therefore, the parathyroid glands lacked stimulation and became atrophic.

In summation, it does appear that there is no specific pituitary parathyrotrophic hormone. Nevertheless, clinical and experimental data are available to support the thesis that the pituitary gland has an indirect effect upon the function of the parathyroid glands by virtue of its influence on the serum phosphate concentration.

Adrenocortical-Parathyroid Interrelationship. Albright and Reifenstein[6] remarked upon the tendency of idiopathic hypoparathyroidism to be associated with Addison's disease. However, as mentioned previously in this report, there are few documented cases noting the coexistence of these rare diseases. No clinical or experimental data are available to indicate that hypofunction of either of these two glands would cause hypofunction of the other gland. On the contrary, experimental and clinical data would suggest that the development of hypoadrenocorticism might ameliorate the effect of hypoparathyroidism and, on the other hand, the administration of adrenocortical hormones might aggravate a hypoparathyroid status. Eppinger, Falta and Rudinger[12] originally pointed out the antagonistic actions of the hormones of the parathyroid and adrenal glands. Guelke[13] confirmed this thesis by demonstrating that adrenalectomy or ligation of the adrenal veins relieved the tetany of hypoparathyroidism. Leifer and Hollander[2] reported that the hypoparathyroidism of their patient subsided with the onset of Addison's disease. They stated, however, that the amelioration may have been due in part to the vitamin D therapy employed. Taylor and Caven[14] reported a sharp rise in the serum calcium levels in animals following adrenalectomy. This rise in serum calcium failed to occur if the animals had previously undergone parathyroidectomy. They also observed that injection of adrenocortical extracts caused a fall in serum calcium. Mirvish and Bosman[15] observed a sharp fall in serum calcium levels of about 30 per cent in twenty-four hours after

injection of adrenocortical extracts into rabbits, with return of the serum calcium levels to normal levels by seventy-two hours. The hypoparathyroid status of Leonard's patient was not ameliorated with onset of Addison's disease. The development of adrenal insufficiency in our patient apparently did not alter the status of the hypoparathyroidism.

More recent studies with cortisone, by Soffer,[16] indicate that cortisone depletes the body calcium by increasing calcium loss in the stool. *A priori*, one would expect that excess cortisone administration would make the management of patients with hypoparathyroidism more difficult. In fact, this has been reported to have occurred. Moehlig and Steinbach[17] observed a patient in whom hypoparathyroidism was well controlled with dihydrotachysterol and calcium lactate therapy. However, when cortisone therapy was started in order to treat the osteoarthritis present, hypocalcemic tetany became uncontrollable despite a marked increase in dosage of dihydrotachysterol and calcium lactate and injection of parathyroid extract. However, three days after discontinuance of cortisone the signs and symptoms of tetany disappeared and the serum calcium rose to within normal limits. Moehlig believes that desoxycorticosterone pellets, too, may cause hypocalcemic tetany. The administration of desoxycorticosterone did not appear to alter the hypoparathyroidism of our patient. Cortisone was not available prior to our patient's death.

Menstrual aggravation of hypoparathyroidism. The authors noted that the frequency of convulsive seizures in our patient appeared to increase before and during the menstrual periods. This has also been reported by Wijnbladh[18] in patients with postoperative tetany. One of his patients noted that she could remain free of tetany if she took vitamin D from the sixth to the third day prior to the expected menstruation. The exact mechanism whereby menstruation causes a temporary decline in the serum calcium is not known to the authors.

Thyroid status in patients with hypoparathyroidism and hypoadrenocorticism. Our patient revealed slightly decreased basal metabolic rate, a normal thyroid uptake of radioactive iodine and a low level of serum protein-bound iodine. These studies would suggest that thyroid function was slightly decreased. Leonard's patient, who had both hypoparathyroid tetany and Addison's disease, had a basal metabolic rate of about minus 10 during the last year of her life. Microscopic examination of the thyroid gland did reveal lymphocytic infiltration. Leifer and Hollander's patient had a basal metabolic rate of minus 9 per cent, later minus 21 per cent. Uptake of radioactive iodine was 14 per cent and, when repeated later, 3 per cent. These data indicate that the thyroid function was in the low range of normal in this patient also. Thus in all three of these cases there seems to have been some decrease in thyroid function and, when the thyroid was examined at necropsy in two of these cases, lymphocytic infiltration was observed.

Although the basal metabolic rate in patients who have uncomplicated Addison's disease is slightly below normal, the uptake of radioactive iodine and the circulating protein-bound iodine are usually normal. However, some reports indicate that marked lymphocytic infiltration of the thyroid gland occurs in patients who have died of adrenocortical insufficiency.[19–21] These changes in the thyroid gland not only included interstitial collections of lymphoid cells but also formation of large areas of lymphoid tissue, frequently with well developed germinal follicles.

SUMMARY

1. The clinical findings, results of metabolic studies and autopsy data on a patient presenting both adrenocortical insufficiency and hypoparathyroidism, are recorded. This is the second known report in which concurrence of these two disorders was established by both clinical and pathologic data. There are published reports of four other similar cases but pathologic data are lacking and some of the clinical data are not complete.

2. The adrenocortical function of the patient in this report was studied before and during adequate therapy for hypoparathyroidism. No apparent difference was noted in the adrenocortical function in the hypocalcemic state when compared with the period of normal serum calcium concentration.

3. Increasing doses of parathormone, up to 500 units per day, failed to alter the level of serum or urine calcium and phosphate. However, when 1,000 units of parathormone were injected per day the concentration of serum calcium rose, serum phosphate fell, and the urinary excretion of both phosphate and calcium rose. Dihydrotachysterol and calcium ingestion resulted in maintenance of normal serum calcium levels.

4. The available data concerning the pituitary-parathyroid interrelationship are reviewed. It would appear that no specific pituitary parathyrotropic hormone has been demonstrated. However, there is evidence to suggest that the pituitary hormones, notably growth hormones, induce a rise in the serum phosphate level and thus stimulate parathyroid activity.

5. The available data concerning the adrenocortical-parathyroid interrelationship are also reviewed. Clinical observations fail to confirm certain experimental data indicating that adrenocortical insufficiency ameliorates the hypoparathyroid state. However, excess cortisone administration may aggravate the manifestations of hypoparathyroidism.

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Pseudohypoparathyroidism*

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IN 1942 Albright and his associates[1] discovered among their patients who apparently had hypoparathyroidism three persons who presented certain clinical features in common and who shared an inability to respond to injections of potent parathyroid hormone. This was considered to represent a failure of end organ response to normal amounts of hormone since biopsy specimens revealed histologically normal parathyroid tissue. They referred to such a situation as an example of "Seabright-bantam syndrome" because the male Seabright bantam has female feathering, presumably as a result of failure of the feathers to respond to normal amounts of male hormone.

Since these cases were reported others have been discovered and the number has increased to approximately twenty-eight.[1–17] This statement is made in order to indicate the relative frequency of the disorder, realizing that such counts are subject to some error.

The syndrome is characterized by tetanic episodes, short stature, a rounded face and abnormally short metatarsals and metacarpals. Soft tissue ossification may occur in the muscles, skin, tendons, basal ganglia and lens. Pseudohypoparathyroidism is more likely to give calcium deposits in skin and basal ganglia than true hypoparathyroidism.[18]

The purpose of this report is to add to available literature our findings in a patient who fulfils the criteria for this diagnosis.

CASE REPORT

The patient, a twenty-three year old Negro man, complained of painful cramping in the feet, hands and wrists.

He had been having cramps, discomfort, and carpopedal spasm as long as he could remember. He had always been small for his age. From earliest childhood he was unable to run and play as much as other children, because exertion produced cramping discomfort in the extremities. This was followed by the typical attitude of carpopedal spasm and led to episodes of unconsciousness several times a month. As the patient grew older he engaged in less activity so that tetanic episodes occurred only once every two or three months. If he ran 100 yards, dyspnea developed, followed by severe cramping pains and stiffness in his feet, wrists and hands; he therefore limited his exercise to prevent discomfort. He served in the Army from 1951 to 1953 and constantly had difficulty performing the required amount of physical exertion. He had numerous physical examinations, but no x-ray examinations were performed and a diagnosis was not established. However, upon medical advice a transfer was arranged to a job which required less physical exertion and symptoms did not recur. Upon re-entering the Army in 1954 the patient began to have pains and cramps in his feet to such a degree that he was seen in orthopedic consultation. Routine x-ray films revealed bony changes and evidence of soft tissue calcification. A tentative diagnosis of pseudohypoparathyroidism was made by one of us (N. Z.) and the patient was admitted to the hospital for further study.

He had had pneumonia at age eight. Because of congenital torticollis a sternomastoid severance and a bone graft from the ilium was performed at age nine. Past medical history was otherwise not remarkable.

Family history was interesting in that his father was of short stature and had very short feet. His paternal grandmother was only 37 inches tall and was described as being small all over.

Systems review revealed no positive information other than poor vision, requiring glasses for ten years, and episodes of diplopia occurring several times a month. The patient's diet had apparently been adequate at all times. He drank about one quart of milk and several quarts of water daily.

Physical examination revealed normal temperature, pulse, respiration and blood pressure. He was 4 feet 11 inches tall and weighed 168 pounds. General appearance was that of a fairly well developed and nourished young Negro man. (Fig. 1.) Skull was

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somewhat flattened posteriorly. Fourth and fifth metacarpals were abnormally short. Thumbs, especially the terminal phalanges, were short and the nails stubby. Third, fourth and fifth metatarsals were short. Eyes revealed no cataracts. Teeth exhibited abnormalities of enamel compatible with hypoparathyroidism. Dentition was irregular and seven teeth were either unerupted or impacted. A small surgical scar 2 inches long was present at the sternal end of the left clavicle. The testes were somewhat small measuring approximately 1 inch by ¾ of an inch. The prostate was smaller than normal to palpation. The body hair and musculature appeared normal. There was a feminine distribution of pubic hair.

A positive Chvostek sign was elicited on one occasion after hyperventilation. Compression of the arm with a blood pressure cuff produced adduction of the thumb within a minute and typical tetanic attitude in three minutes.

Psychiatric evaluation revealed no evidence of mental retardation.

Blood counts were within normal limits except for a lymphocytosis, ranging from 57 to 64 per cent, in four of six determinations. The serologic test for syphilis gave a negative result. Several urinalyses were within normal limits and a specific gravity of 1.020 was found on two random specimens. The total twenty-four-hour urinary calcium excretion was measured on five occasions, being 22, 44, 15, 22 and 15 mg., respectively. The twenty-four-hour urine phosphorus excretion was 275, 445, and 291 mg. on three separate days. The total output of 17-ketosteroids in a twenty-four-hour urine collection was 6.1 mg. (normal 13 to 26 mg.).

Serum calcium ranged from 7.1 to 7.5 on four determinations. At the same time the serum phosphorus ranged from 5.2 to 5.7 mg. The serum alkaline phosphatase was 3.3 Bodansky units. Serum sodium was 128 mEq./L., potassium 3.9 mEq./L. and carbon dioxide combining power 63 vol. per cent. Blood urea nitrogen was 11 mg. per cent. Serum albumin was 3.1 gm. per cent and serum globulin was 2.9 gm. per cent. An absolute eosinophil count was 112 per cu. mm. A glucose tolerance test revealed a fasting level of 91 mg. per cent. Hourly samples taken after the oral ingestion of 100 gm. of glucose revealed 87, 83, 102 and 85 mg. per cent, respectively.

Electrocardiogram showed no abnormalities. Basal metabolic rate determination was −22 per cent.

Reports of roentgenograms (September 10, 1954) were as follows: Skeletal survey: bones show a coarse trabecular pattern which is suggestive of a metabolic abnormality. In the skull there are brachycephaly, sclerotic petrous ridges, prognathous jaw with dental deformities (impacted unerupted molars and marked overbite), but no evidence of intracranial calcification. In the hands, there are deformities and shortening of the fourth and fifth metacarpals bilaterally and of the first metacarpal on the right. In the feet there are

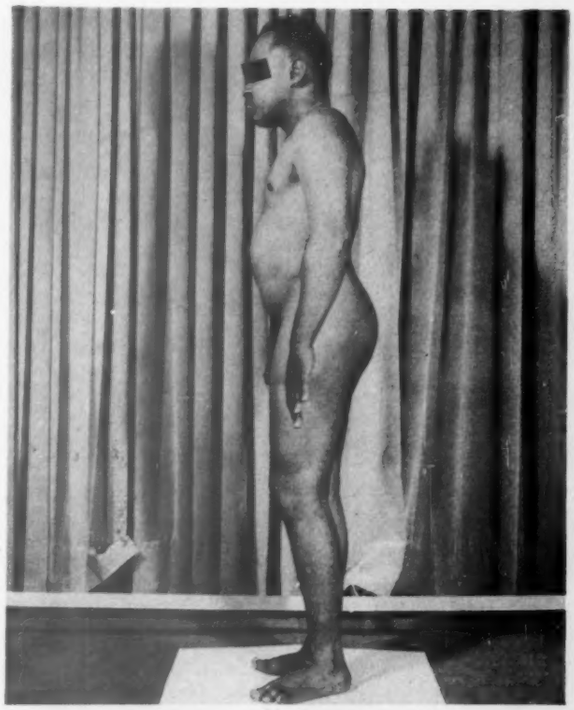

FIG. 1. General appearance of the patient. Note the setback position of the fourth and fifth fingers and the third, fourth and fifth toes. (U. S. Army photograph.)

shortening and deformity of the third and fourth metatarsals. (Fig. 2.) The tibias show a porous trabecular pattern, especially marked in the epiphyseal region. (Fig. 3.)

Noted in the survey are flecks of calcification in the soft tissues which are mostly subcutaneous but some of which seem to lie in tendons. They are particularly heavy in the feet, legs and knees, but some are noted in the hands and in the pelvis overlying the shadow of the lower sacrum. Occasional flecks are noted in the skin of the thorax and thighs. Chest: heart and lungs were normal. Abdomen: appearance was normal aside from the bone changes seen in the skeleton as a whole and the calcifications in the pelvis noted previously.

An intravenous pyelogram revealed no abnormalities.

During observation in the hospital the patient wae asymptomatic except for cramping sensations in the feet and hands which occurred once or twice a week, each time associated with physical exertion. When the diagnosis was established, he was given a diet devoid of milk (because of its phosphorus content) and took aluminum hydroxide gel with each meal. He was also given dihydrotachysterol, 1 cc. three times daily, until the Sulkowitch reaction became positive. Approximately after one week of treatment there had been little change in symptoms, and it became necessary to separate the patient from military service. Therefore further observation was not possible.

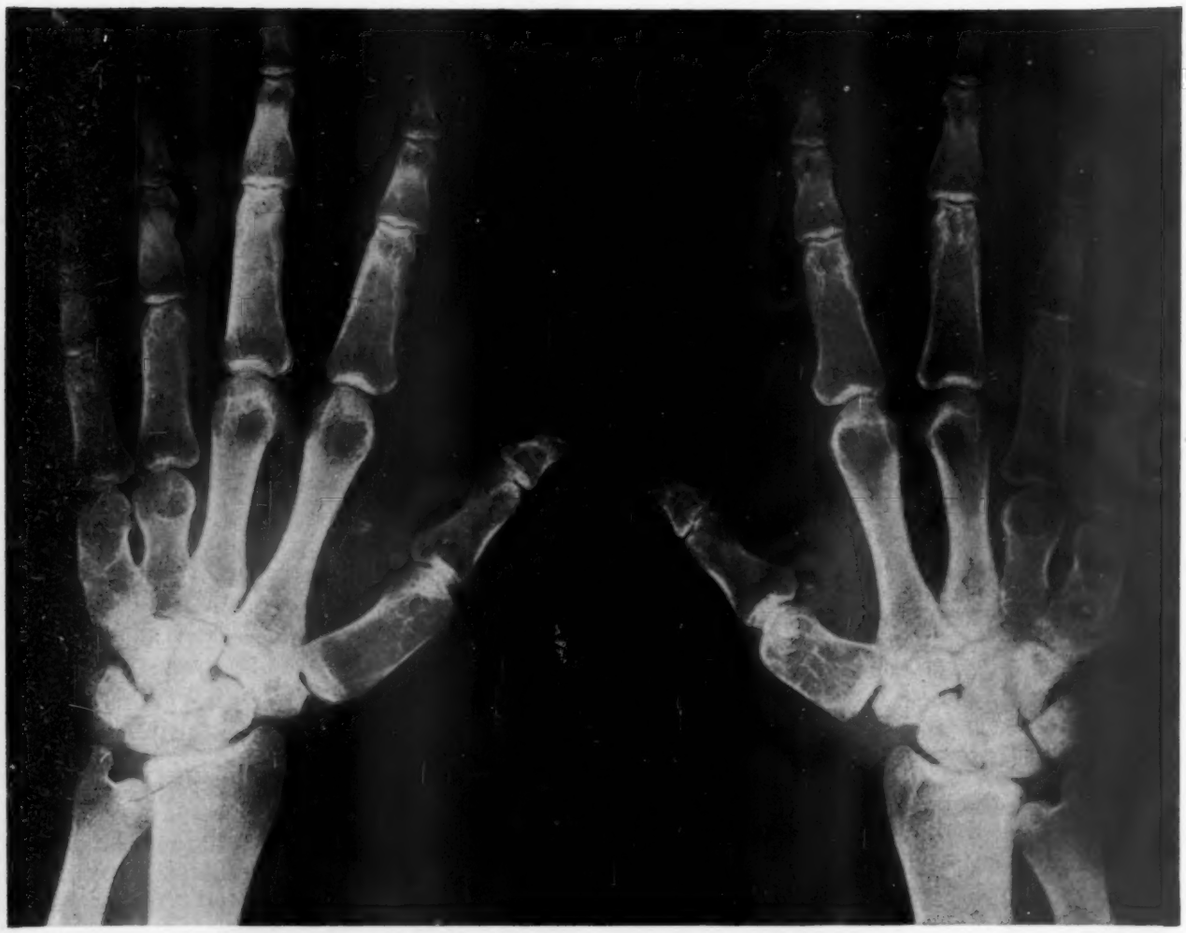

FIG. 2. Roentgenogram of the hands illustrating the coarse trabeculation, soft tissue calcium, and shortening of the fourth and fifth metacarpals of each hand, and of the first metacarpal on the right. (U. S. Army photograph.)

COMMENT

The recognition of pseudohypoparathyroidism as an entity is amply justified on the basis of both clinical and laboratory observations over the past thirteen years. Its relative rarity is indicated by the fact that less than thirty cases have been reported in that period, although it is quite likely that other cases escaped detection or were unreported. The peculiar physiognomy and resemblance of the patients to one another was pointed out in the original article[1] and has been confirmed by subsequent observers. Such an observation is difficult to evaluate but seems to follow a pattern reminiscent, for example, of mongolism. It has been suggested that pseudohypoparathyroidism might be a mutation in one gene which controls several apparently unrelated traits.

Pseudohypoparathyroidism presents the same general findings as hypoparathyroidism due to other causes, in that both types will display manifestations of tetany, low levels of serum calcium, high levels of serum phosphorus and in some instances deposits of calcium in the basal ganglia. Patients with pseudohypoparathyroidism, however, are distinguished by four findings: (1) round faces and short thick-set figures; (2) shortening of some of the metacarpals and metatarsals; (3) subcutaneous foci of ectopic ossification and (4) failure to respond to injections of potent parathyroid extract which normally will produce a phosphate diuresis. All four of these findings are not necessarily present in each case; a few instances of the occurrence of abortive cases which manifest only a portion of the syndrome have been recorded. Albright has observed cases with unresponsiveness to the parathyroid hormone without the other features of the syndrome. He has likewise encountered patients who failed to respond to the hormone

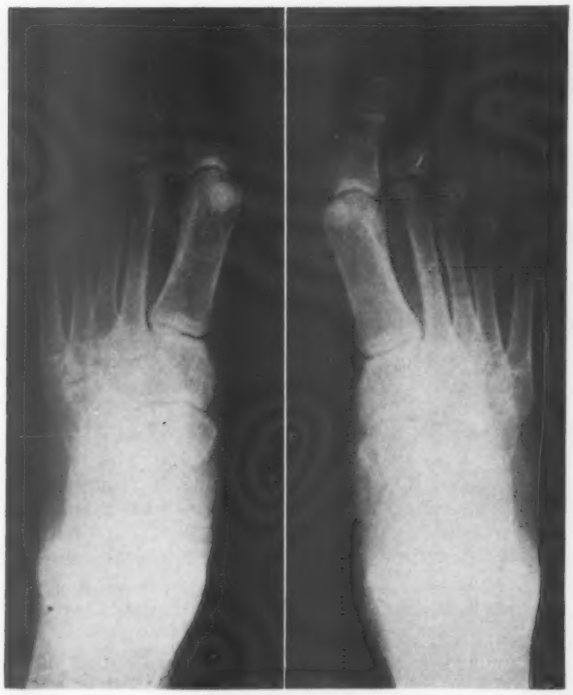

FIG. 3. Roentgenogram of the feet illustrating the characteristic shortening of the third and fourth metatarsals together with flecks of calcium in the soft tissues. Note the deposit near the metatarso-phalangeal joint of the right great toe. (U. S. Army photograph.)

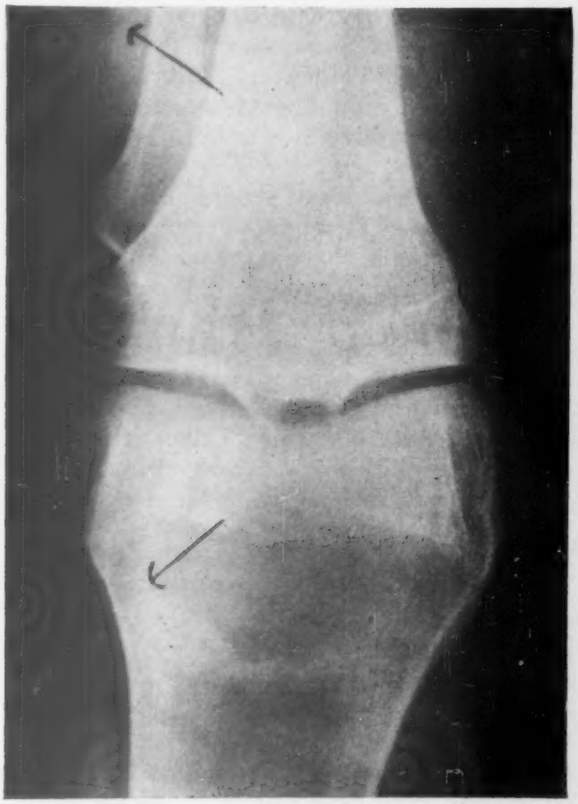

FIG. 4. Roentgenogram of the knees illustrating flecks of calcium in the soft tissues. (U. S. Army photograph.)

and had round faces and short statures but lacked the other manifestations. In 1952 a case of "pseudo-pseudohypoparathyroidism" was reported;[13] all features of the syndrome were present except low serum calcium and elevated phosphorus.

A comparison of the features and habitus of our patient (Fig. 1) with others in the literature will confirm the general resemblance of these patients to one another. The similarity to the patient reported by Reynolds et al.[12] is particularly striking. In addition to the short stature and rounded face, shortness of the metacarpals is an easily recognizable physical finding which does not occur in the idiopathic form. A simple test for this feature is to have the patient clench his fist.[13] The knuckle prominence will be apparent at the normal metacarpophalangeal joints, but will be deficient or recessed at the other knuckles due to shortening of the metacarpals. Epiphyseal closure in the metacarpals occurs in the order I, V, IV, III and II. A general rule based on this fact is that if any metacarpal is involved I will be. If two are involved, they will be I and V, and so on. It will be seen (Fig. 2) that metacarpal I on the left hand of our patient is affected very little in spite of the shortening of metacarpals IV and V. Similar general rules apply to the metatarsals, but metatarsal IV appears to be affected first.[13]

The finding of ossification in the soft tissue and in the basal ganglia is somewhat more common in the pseudo-form of hypoparathyroidism than in the idiopathic variety. These findings, along with the skeletal changes, are such that the diagnosis is usually suspected first by the radiologist. (Figs. 3 and 4.) In this connection it should be noted that the term calcification is not strictly accurate since biopsy specimens show bone formation,[13] so that the term ossification is preferable. Alexander and Tucker observed cells resembling hemopoietic elements along with the ossification in their patient.[4]

Our patient had a flat glucose tolerance curve as did the patient reported by Reynolds et al.[12] There was no diarrhea or other gastrointestinal disturbance to explain this finding. The cases of Berardinelli[11] and Moehlig and Gerisch[7] by contrast had a diabetic type of glucose tolerance curve. It may be of interest that our patient

had the firmly entrenched habit of drinking large volumes of water, as did the patient of Reynolds et al.[12] However, the urine concentrated normally on several occasions. A low level of 17-ketosteroids has been encountered by others.[12]

The occurrence of the syndrome in twins has been reported.[16] These girls were noted to have calcific plaques in the abdominal wall at birth. They both had internal strabismus, mental retardation and characteristic changes in serum calcium and phosphorus. Roentgenograms at age five revealed evidence of beginning closure of the fourth metacarpal. Both patients responded to A.T.10 therapy. Talbot et al. point out the possibility that cerebral edema accompanying hypocalcemia could partly account for the mental retardation as well as pressure effects on the sixth cranial nerve in its course along the base of the skull. Elrick et al.[8] also studied a twin with the syndrome and it appeared probable that the other twin was affected. Mackler et al.[15] reported two cases in one family.

Tests of urinary phosphorus excretion were carried out by the Ellsworth-Howard method[19] on three separate occasions, along with a different normal control in each instance. Para-thor-mone® doses of 200 mg. intramuscularly were used on two occasions. In the second test 300 mg. were given intravenously. The results were quite variable and not reproducible, although a fresh supply of para-thor-mone was purchased for the last test to ensure potency of the preparation. This has been the experience of others.[14,17] Albright, who has reviewed our findings and confirmed the diagnosis, has stated that the Ellsworth-Howard test is quite unreliable in the differentiation of pseudohypoparathyroidism from hypoparathyroidism.[21] As an alternative he suggested daily intramuscular injections of para-thor-mone for a number of days after which serum calcium and phosphorus levels could be determined.

SUMMARY

A young Negro man is described who fulfils the criteria for a diagnosis of pseudohypoparathyroidism. Less than thirty such cases have been reported.

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Dyschondroplasia with Soft Tissue Calcification and Ossification, and Normal Parathyroid Function ("Pseudo-pseudohypoparathyroidism")*

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IN 1942 Albright and associates[1] reported a small group of cases in which the patients presented the clinical and biochemical syndrome of idiopathic hypoparathyroidism and in addition were found to have certain special physical characteristics: short stature, round face and brachydactylia due to shortening of certain metacarpals. These patients did not respond with the expected phosphorus diuresis when given intravenous parathyroid hormone, and in two subjects the parathyroids were examined and found to be hyperplastic.[2] Albright suggested that these patients had normal parathyroid hormone production but that the end organ (the kidney) was unable to respond normally. The term "pseudohypoparathyroidism" (Seabright-bantam syndrome) was coined to describe these cases. Approximately twenty-four cases conforming to the criteria indicated have since been reported.[3–7]

The relationship of the special physical characteristics of these patients to the abnormality of their calcium metabolism is not certain. In 1952 Albright and others described a young woman who exhibited these physical characteristics, as well as soft tissue calcification and ossification, but who had normal serum calcium and phosphorus levels and no symptoms of hypoparathyroidism.[8] Albright termed this entity "pseudo-pseudohypoparathyroidism." A second instance of this syndrome, again in a young woman, was reported by Miles and Elrick,[9] and a report of a third case, in a man, has recently appeared.[10] The present report is of a young adult man who exhibited brachydactylia due to short metacarpals, short stature, and soft tissue calcification and ossification, together with normal serum calcium and phosphorus levels and a normal response to calcium infusion.

CASE REPORT

J. R. G. (No. 20673), a twenty-four year old white male hospital orderly, was admitted on March 8, 1955, because of pain and stiffness of nine months' duration of the left knee.

The patient was born in 1930, without known trauma, and weighed five pounds. Gestation had been considered of normal length. Early development appeared normal but at age four or five he was noted to have unusual hands and feet and high pedal arches. At that time he was admitted to another hospital because of scarlet fever and otitis media; the hospital record made no note of skeletal abnormality. When in the third grade at school, he was transferred to a special retarded class where manual arts were emphasized.

At age thirteen he was struck on the head by a rock, sustaining a fracture of the left temporoparietal region without apparent brain damage. The hospital record stated: "There is a curious defect of fingers and toes, all the digits being approximately the same length." At age fifteen he was seen at an endocrine clinic where a diagnosis of "dwarfism, type not determined" was made. Thyroid extract was administered without definite response. An attempt at testosterone pellet implantation was unsuccessful. At seventeen he was seen in another clinic because of his short stature and poor mental development. A diagnosis of dyschondroplasia was made but no treatment was recommended. Serum calcium and phosphorus determinations were not done.

The patient complained of a variety of symptoms

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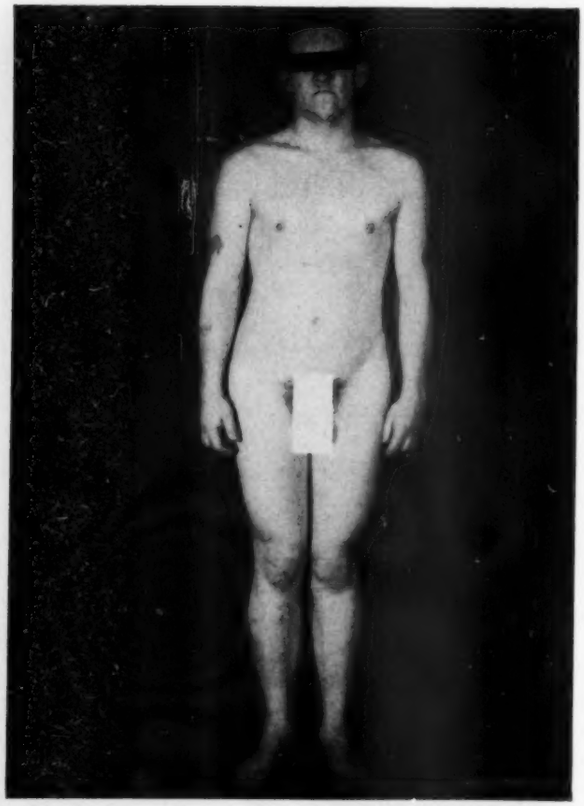

FIG. 1. Full view of the patient. The face, although broad, is not especially rounded.

which he dated in onset either to the time of his skull fracture or to approximately two years prior to this admission. These included left-sided headaches, weakness on arising suddenly, transient shooting pains in the extremities, and tinnitus. On several occasions the patient had episodes of unconsciousness following the ingestion of twelve to fifteen glasses of beer. These began with an upward movement of the eyes; he would then fall to the floor and remain unconscious until transported home. Urinary incontinence had occurred on several occasions, fecal incontinence once, and on one occasion convulsive movements were described. He never injured himself and never had any such episodes except after drinking. There were no gastrointestinal symptoms. For several years the patient had consumed an average of three quarts of milk daily. He described himself as too shy to go out with girls but capable of erections and nocturnal emissions. His pubic hair and beard appeared at age seventeen and he shaved every three days.

Family history did not reveal consanguinity. The patient was the youngest of eight children, all of whom had normal physical and mental development. His shortest sister was sixty-six inches tall, his shortest brother seventy inches. None of the family had any skeletal or endocrine abnormalities and all had thinner faces and thinner noses than the patient. There was no family history of seizures.

The patient's present illness dated back nine months prior to admission. At that time he began to note pain and stiffness in his left knee. Six months prior to admission a portion of the meniscus was removed surgically on that side. Shortly thereafter he was accepted by the Air Force, after having been rejected several times previously because of his short stature and poor mental development. He was physically unable to complete basic training and received a medical discharge after two months in service. Because of persistent pain in the knee he was referred to this hospital for further care.

Physical examination on March 8, 1955, revealed a temperature of 98.6°F., pulse 96, respirations 14, blood pressure 125/75. The patient was sixty-two and a half inches tall (pubis to floor thirty-three and one-half inches, span sixty and one-half inches) and weighed 128 pounds. He was a small, well proportioned and well developed young man appearing younger than his stated age. (Fig. 1.) His face was broad but not round. He was pleasant and cooperative although somewhat slow mentally. A linear scar was present over the left temple. The eyes were normal. Slit lamp examination revealed no corneal or lenticular opacities. Although a few teeth were missing, the remainder appeared normal. The heart showed a grade 1 blowing precordial systolic murmur which was thought to be functional. The genitalia and pubic hair appeared normal. Neurologic examination was entirely normal; neither Chvostek nor Trousseau signs could be elicited. The appearance of the fingers and hands is illustrated in Figure 2. The second, third and fourth fingers were approximately of equal length; the first and fifth fingers were hyperextensible bilaterally. The second, third, fourth and fifth toes were also hyperextensible. The nails were rather short, with fine vertical ridging. When the patient made a fist, the metacarpophalangeal joints were not prominent and actually indented over the fourth and fifth knuckles.

Laboratory data were as follows: urinalysis revealed a specific gravity of 1.020, pH 5.0; there was no albumin or sugar; microscopically no formed elements were noted. Hemoglobin was 12.9 gm. per 100 ml. The total and differential white blood cell counts were normal. Serologic test for syphilis gave a negative result. Blood non-protein nitrogen was 44 mg. per 100 ml., serum alkaline phosphatase 1.9 Bodansky units. Total serum protein was 6.8 gm. per 100 ml. The electrocardiogram showed only left axis deviation.

An electroencephalogram with photic stimulation showed diffuse, non-focal, slow wave activity with moderate build-up on hyperventilation. Repetition of the tracing with hyperventilation after the injection of 20 cc. of 10 per cent calcium gluconate intravenously, showed no appreciable diminution in the non-focal slow wave pattern. Psychometric examination disclosed a verbal I.Q. of 72 contrasted with a

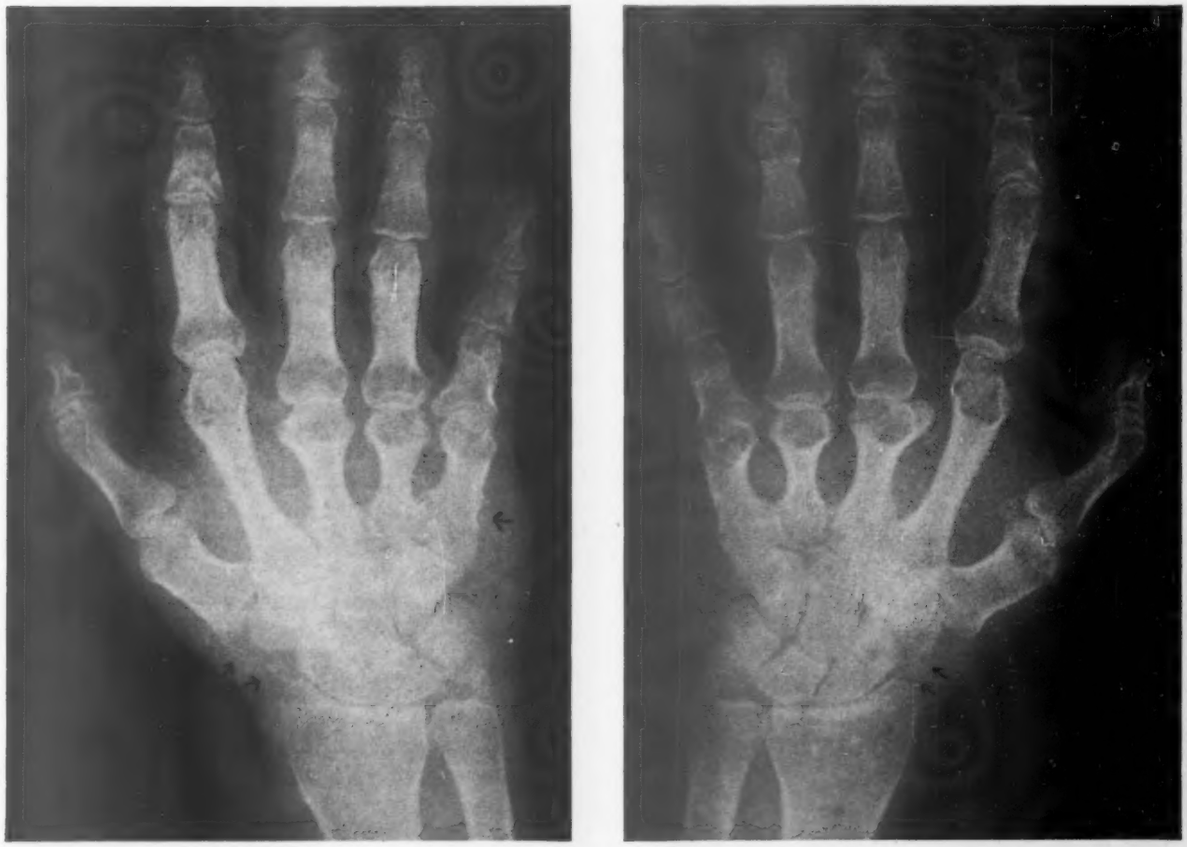

FIG. 2. Roentgenograms of hands, showing shortened metacarpals and phalanges. The arrows point to areas of soft tissue ossification readily seen in the original films.

spatial I.Q. of 99. The dissociation was thought to be at least in part related to the dominant emphasis on manual training in his education.

X-rays of the hands showed bilateral shortening of the first, third, fourth and fifth metacarpals, the proximal phalanges of the fifth digits, the middle phalanges of the second and fifth and the terminal phalanges of first and third. (Fig. 2.) In the feet, the fourth and fifth metatarsals on the right, the first metatarsal on the left and the proximal phalanges of the great toes bilaterally were shortened. There was some irregularity of the trabecular pattern, particularly in the shortened bones.

The soft tissues of the hands, wrists, legs and feet showed small streaks of calcification and ossification. This was particularly marked in the soft tissues of the plantar aspects of the feet. A small exostosis arose from the mid-portion of the right radius.

The skull showed no intracranial calcification. There was slight prognathism, and several of the molar and premolar teeth were missing. The lamina dura was intact. There was a mild coxa vara deformity and some flattening of the heads of the femora, partial obliteration and some sclerosis of the sacroiliac joints. The bodies of cervical, thoracic and lumbar vertebrae showed biconcave impressions in their posterior halves.

SPECIAL STUDIES

While the patient was on a test diet containing 125 mg. calcium daily, the serum calcium[11] levels were 8.6 to 8.7 mg. per 100 ml., serum inorganic phosphorus[12] 3.3 to 4.1 mg. per 100 ml., and urinary calcium excretion 65 and 75 mg. per twenty-four hours on two successive days. These values are within the normal range.

The response to an infusion of calcium salt, performed as described by Howard and associates[13] and by Nordin and Fraser,[14] was also examined. (Fig. 3.) After the infusion of 940 mg. of calcium (as the gluconate-glucoheptonate) over an interval of three and a half hours, the serum concentration of calcium and phosphorus rose from 8.60 and 3.66 to 13.5 and 5.0 mg. per 100 ml., respectively, and then slowly returned to control values. Urinary calcium excretion increased so that an amount equivalent to approximately one-half of the infused calcium was

excreted in the first twenty-four hours; however, phosphorus excretion decreased despite the elevated serum level. This is a normal response which has been explained in the following way: a decrease in secretion of endogenous parathyroid hormone is believed to occur in response

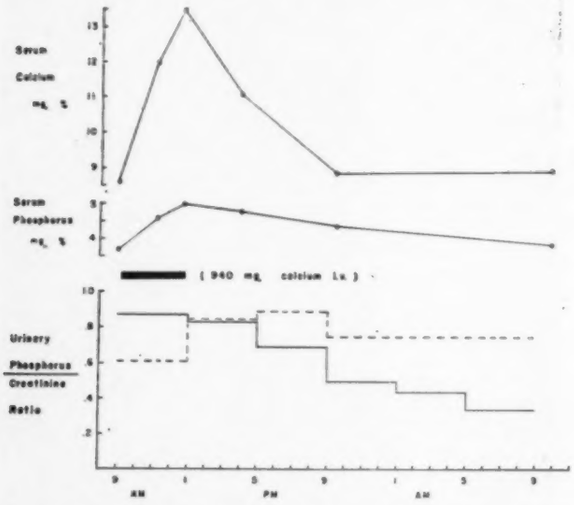

FIG. 3. Response to calcium infusion. Urinary phosphorus excretion is expressed as phosphorus/creatinine ratio to minimize any error in urine collection when the patient was not under direct observation. The dotted line represents urinary phosphorus/creatinine ratio during the twenty-four hour control period immediately preceding the test day.

to an elevated serum calcium level. As a consequence of the decrease in circulating hormone, the renal tubules reabsorb more phosphate, and its excretion is thereby diminished.[13] Alternative explanations also may be offered.

The patient's response to an intravenous injection of parathyroid extract was examined by a modification of the Ellsworth-Howard test.[15] As usually performed, the test consists of a comparison of the phosphorus excretion for three hours before and five hours after the intravenous injection of 200 U.S.P. units of parathyroid extract. There is a normal diurnal variation of phosphorus excretion consisting of a sharp fall in the early morning followed by a rise to peak rate at about noon; excretion is then maintained or falls off gradually during the afternoon, remaining well above the morning level.[16–18] In the present instance the test was arranged so as to avoid mistaking this late morning rise for an effect of parathyroid hormone. The patient had a light breakfast, then remained recumbent except to void hourly, taking nothing by mouth except water for the duration of the experiment. Two hundred U.S.P. units of parathyroid extract (Lilly) were injected intravenously at 1:00 P.M., at a time when phosphorus excretion was already rising. A small transient increase in phosphaturia resulted which seems consistent with a normal

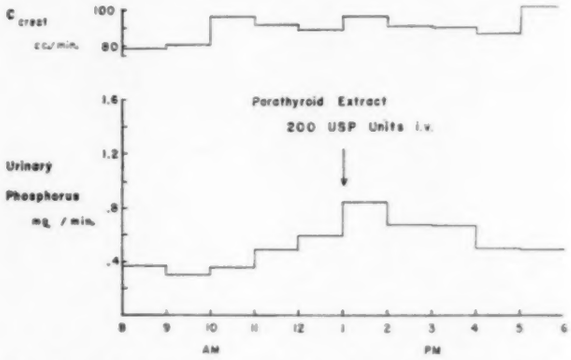

FIG. 4. Patient's Ellsworth-Howard test. Clearance of endogenous creatinine plotted above, as index of glomerular filtration rate as well as an indicator of complete bladder emptying.

diurnal curve. The diurnal change in phosphorus excretion appeared to result from a decrease in tubular reabsorption of phosphorus. There was no change in clearance of endogenous creatinine (Fig. 4) or in clearance of inulin and para-aminohippurate.

In a normal subject the same lot of extract was used in a two-day test, the first day serving as a control. The subject occupied himself with light office work, keeping walking to a minimum. Meals were taken at 8:30 A.M., 12:30 P.M. and 5:30 P.M., and were estimated to provide 240 mg. calcium and 800 mg. phosphorus per day. The menu for the first day was identical with that for the second day. When parathyroid hormone was given on the second day at 3:00 P.M. after phosphorus excretion had stabilized, no further increase in excretion was observed during the next five hours. (Fig. 5.)

COMMENT

The diagnosis of pseudohypoparathyroidism was considered in this case because of the patient's short stature, broad face, poor mental development, short metacarpals and sub-cutaneous calcification. The patient's history of seizures might possibly have been related to hypocalcemia. Studies revealed no abnormality of calcium metabolism however. This

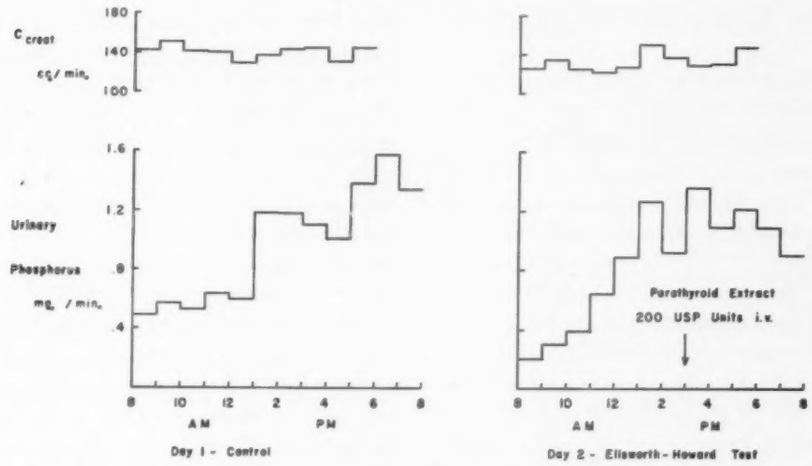

FIG. 5. Ellsworth-Howard test performed on a normal subject, over two successive days. The diurnal rise in phosphorus excretion is clearly shown.

patient therefore represents a fourth case of pseudo-pseudohypoparathyroidism.

Although the metacarpal shortening seen in this patient is encountered in association with the disordered calcium and phosphorus metabolism characteristic of pseudohypoparathyroidism, the lack of an obligatory relationship of this special form of dyschondroplasia to the metabolic disorder was indicated by Albright and associates[8] when they encountered this abnormality in a patient whose serum calcium and phosphorus levels were both normal. Miles and Elrick's case[9] showed, in addition to metacarpal shortening, lenticular opacities, mental deficiency and diffuse electroencephalographic abnormalities. All of these are often ascribed to defective parathyroid function with accompanying hypocalcemia. However, no such abnormality was present in Miles and Elrick's case at the time of study.

It appears that the two syndromes, pseudohypoparathyroidism and pseudo-pseudohypoparathyroidism, comprise a group of defects which tend to occur together but are not necessarily interrelated. There are reported cases of pseudohypoparathyroidism in which one or more of these defects is absent.[1,2] Similarly, not all of the physical defects found in the pseudohypoparathyroid group are seen in all four of the cases of pseudo-pseudohypoparathyroidism thus far reported. (Table I.)

The presence of normal serum calcium and inorganic phosphorus values on a diet low in calcium, and the normal urinary calcium excretion in this patient are the most cogent points in favor of normal parathyroid function. The response to intravenous calcium is confirmatory. Howard and associates[13] found a rise in serum phosphorus and a fall in urine phosphorus after calcium infusion in normal subjects, comparing the twenty-four-hour phosphorus excretion on the day of the calcium infusion with the preceding and following control days. In patients with hypoparathyroidism the twenty-four-hour urinary phosphorus excretion rose after calcium infusion. Nordin and Fraser[14] presented data obtained from normal subjects, all of whom showed a fall in phosphorus excretion on infusion of calcium salts. Their average normal curve closely approximated the response obtained in our patient, while in two hypoparathyroid pa-

TABLE I

TABULATION OF CLINICAL FEATURES IN FOUR CASES OF PSEUDO-PSEUDOHYPOPARATHYROIDISM

Findings	Case 1[8]	Case 2[9]	Case 3[10]	Present Case
Age and sex	29, F	24, F	40, M	24, M
Round face	+	+	±	±
Short stature	+	+	+	+
Lenticular opacities	0	+	+	0
Mental deficiencies	−	+	−	+
Normal serum calcium and phosphorus	+	+	+	+
Electroencephalographic changes	−	+	−	+
Short metacarpals	+	+	+	+
Short metatarsals	+	+	−	+
Exostoses	−	0	+	±
Mild coxa vara	−	+	−	+
Subcutaneous calcification	+	0	0	+
Calcification of basal ganglia	0	0	0	0

Note: + = present, 0 = absent, − = no observation.

tients they found no decrease in phosphorus excretion.

The expected response to parathyroid hormone injection (Ellsworth-Howard test) consists of an increase of phosphorus excretion in normal persons and an even greater increase in patients with idiopathic hypoparathyroidism, while in patients with pseudohypoparathyroidism no increase should be seen.[19] In recent years, however, there have been several instances in which urinary phosphorus excretion failed to increase in normal subjects after administration of parathyroid extract.[7,20,21] A possible explanation for this discrepancy can be raised but requires some comment on present knowledge of parathyroid physiology. It appears fairly well established that endogenous parathyroid hormone acts on the kidney to increase phosphorus excretion. This is reflected indirectly in the low phosphorus clearance seen in clinical hypoparathyroidism in man,[20] as well as following parathyroidectomy in the experimental animal.[22,23] In hyperparathyroidism the opposite situation exists, urinary phosphorus clearance being higher than normal provided renal function is not too greatly impaired.[24] The majority of studies suggest that the increased phosphorus excretion following administration of parathyroid extract is primarily a result of a decrease in renal tubular reabsorption of phosphorus.[22,24–26]

It also appears established that there is a second action of parathyroid hormone, perhaps the more important one, to mobilize calcium directly from bone. The frequency of skeletal demineralization in hyperparathyroidism is well recognized, at least when dietary calcium intake is not high, and localized demineralization can be produced experimentally by implanting parathyroid tissue in direct contact with bone.[27] In experiments which excluded any associated renal mechanism, Stewart and Bowen have shown parathyroid extract to be capable of restoring the level of serum calcium when it had been previously lowered by injection of oxalate salts into parathyroidectomized-nephrectomized dogs.[28] Since good evidence does not exist for an effect of the parathyroids on calcium absorption and excretion in the gastrointestinal tract these studies in nephrectomized animals demonstrate fairly conclusively a direct action on bone.[29]

There is increasing evidence that these two actions of the parathyroids may be separable and independent. Stewart and Bowen[30] have shown that formaldehyde-treated extracts which were inactive as judged by effect on serum calcium level were still effective in producing a phosphorus diuresis in dogs. In addition, Kenny and associates[31] have prepared an extract which exhibited an even higher phosphaturic effect per unit of serum calcium elevation in rats than did a standard commercially-available extract tested in the same manner. Because of these independent actions, the effect of parathyroid extract on renal phosphorus excretion may not necessarily be closely correlated with its U.S.P. potency as bioassayed by effect on serum calcium level in the dog. It is possible that unrecognized changes in the commercial extraction procedure may explain the lack of effect on urinary phosphorus which is sometimes noted.

The Ellsworth-Howard test must also be examined against the background of a considerable diurnal variation in urinary phosphorus output. This is well known but appears to have been neglected by investigators of parathyroid function. The pattern of high nocturnal excretion with morning fall, usually shortly after arising, and gradual rise toward noon, has been well described.[16,18] This diurnal cycle can be altered by reversal of the sleep-wake pattern, institution of a twelve-hour routine, ingestion of high-carbohydrate meals, administration of insulin, changes in posture, and brisk activity.[18,32–34] The role of the parathyroid glands in establishing or maintaining this cycle is not known. No studies of diurnal variation in hypoparathyroid patients have been encountered, although the authors have recently observed a late morning rise in phosphorus excretion in one subject with idiopathic hypoparathyroidism. The effect of these normal changes on the interpretation of the Ellsworth-Howard test is obvious. When the test is used, it might be preferable to administer the parathyroid extract in the afternoon or early evening. The diurnal cycle does not usually produce changes of such magnitude as have been described in hypoparathyroid patients, in whom tenfold and greater increases in phosphorus excretion were obtained.[19] It is possible that the hypoparathyroid patient, like the patient with myxedema, is more sensitive to the missing hormone than is the normal subject. On the other hand, these large increases may depend simply on the high serum phosphorus level in hypoparathyroid patients, and have no greater significance than does this level in itself.

SUMMARY

A twenty-four year old white man with short stature, short metacarpals, subcutaneous calcification and ossification but with normal parathyroid function is presented. The patient fulfill the criteria for the diagnosis of pseudo-pseudohypoparathyroidism, being the fourth case to be reported.

Studies of calcium and phosphorus metabolism, including calcium infusion and intravenous parathyroid extract administration (Ellsworth-Howard test), were performed. Difficulties in the evaluation of these tests, particularly the Ellsworth-Howard test, are discussed. An increase in urinary phosphorus excretion cannot be attributed to administration of parathyroid extract unless the normal diurnal rise in urinary phosphorus has been taken into account. On the other hand, failure of phosphorus excretion to change after injection of parathyroid extract may on occasion be due to variations in the extract rather than to an abnormal renal response.

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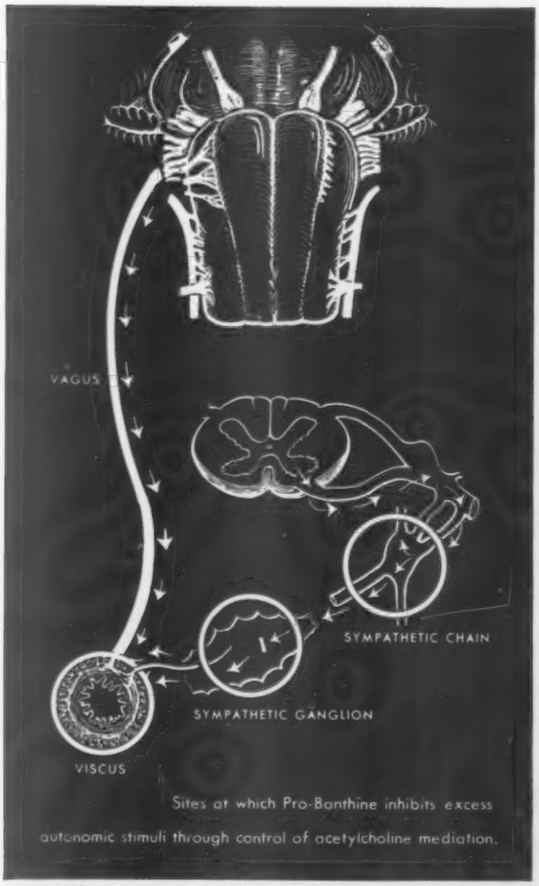
PRO-BANTHĪNE® FOR ANTICHOLINERGIC ACTION

A Combined Neuro-Effector and Ganglion Inhibitor

Pro-Banthīne consistently controls gastrointestinal hypermotility and spasm and the attendant symptoms.

Pro-Banthine is an improved anticholinergic compound. Its unique pharmacologic properties are a decided advance in the control of the most common symptoms of smooth muscle spasm in all segments of the gastrointestinal tract.

By controlling excess motility of the gastrointestinal tract, Pro-Banthine has found wide use[1] in the treatment of peptic ulcer, functional diarrheas, regional enteritis and ulcerative colitis. It is also valuable in the treatment of pylorospasm and spasm of the sphincter of Oddi.



Sites at which Pro-Banthine inhibits excess autonomic stimuli through control of acetylcholine mediation.

Roback and Beal[2] found that Pro-Banthine orally was an "inhibitor of spontaneous and histamine-stimulated gastric secretion" which "resulted in marked and prolonged inhibition of the motility of the stomach, jejunum, and colon. . . ."

Therapy with Pro-Banthine is remarkably free from reactions associated with parasympathetic inhibition. Dryness of the mouth and blurred vision are much less common with Pro-Banthine than with other potent anticholinergic agents.

In Roback and Beal's[2] series "Side effects were almost entirely absent in single doses of 30 or 40 mg. . . ."

Pro-Banthine (β-diisopropylaminoethyl xanthene-9-carboxylate methobromide, brand of propantheline bromide) is available in three dosage forms: sugar-coated tablets of 15 mg.; sugar-coated tablets of 15 mg. of Pro-Banthine with 15 mg. of phenobarbital, for use when anxiety and tension are complicating factors; ampuls of 30 mg., for more rapid effects and in instances when oral medication is impractical or impossible.

For the average patient one tablet of Pro-Banthine (15 mg.) with each meal and two tablets (30 mg.) at bedtime will be adequate. G. D. Searle & Co., Research in the Service of Medicine.

---

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Clinical trial packages of Pro-Banthīne and the new booklet, "Case Histories of Anticholinergic Action," are available on request to . . .

SEARLE

P. O. Box 5110-C-2
Chicago 80, Illinois

Meat...

and Its Place in the Diet in Congestive Cardiac Failure

Meat has an appropriate place in the moderate-protein, low-sodium, acid-ash diet advocated in the dietary management of patients with congestive cardiac failure.[1] When extreme sodium restriction is necessary, the meat allowance is regulated accordingly.

Lean meat allows maintenance of a positive nitrogen balance without excessive protein intake, because its amino acids match the quantity and proportions needed for tissue synthesis and repair.[2,3] In the fresh state as purchased it supplies only small amounts of sodium ranging from approximately 50 to 100 mg. per 100 grams. Due to its acid-ash composition (equivalent to 4 to 38 ml. of normal acid per 100 grams of meat) it may facilitate diuresis.[1]

In addition to these important features, meat contributes valuable nutritional factors by virtue of its generous supply of high quality protein, B vitamins, and essential minerals—iron, phosphorus, potassium, and magnesium.

Easy digestibility, a prime requisite of foods eaten by the patient with congestive cardiac failure, is another outstanding quality of meat.

---

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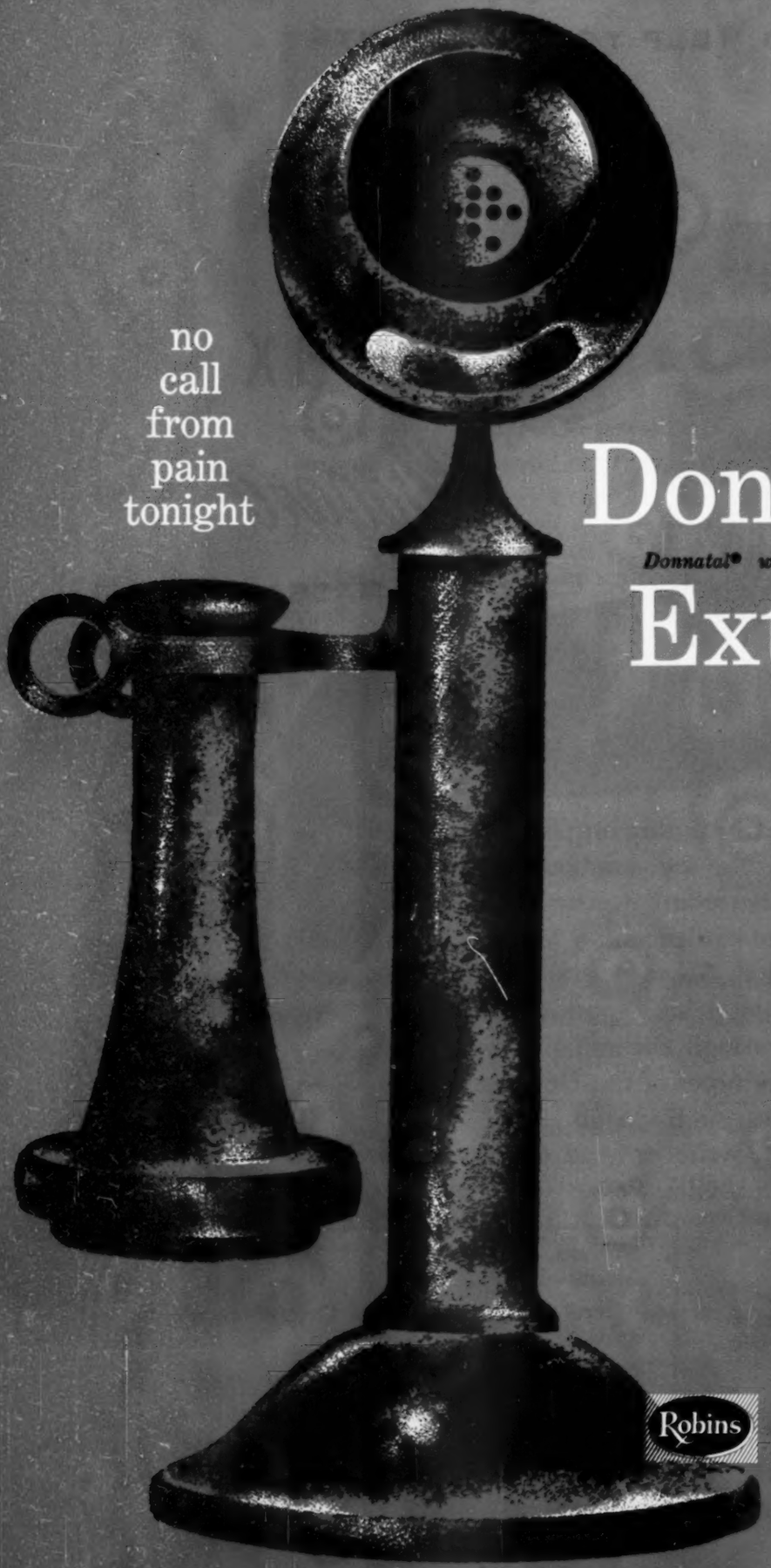
The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

for the first time...extended action codeine



no call from pain tonight

10 to 12 hours uninterrupted pain relief in a single tablet

Donnagesic™

Donnatal® with Codeine extended action tablets

Extentabs

- no up-and-down analgesia
- better codeine toleration

Belladonna alkaloids and phenobarbital, as in Donnatal, induce mild sedation, reducing pain consciousness and anxiety. Patient is protected from spasm. Codeine constipation, nausea and vomiting are avoided. Phenobarbital directly augments the potent analgesic effect of codeine.[1] Indicated wherever codeine is indicated—in pain or cough.

Donnagesic No. 1 (pink)

CODEINE Phosphate (¼ gr.)	48.6 mg.
Hyoscyamine Sulfate	0.3111 mg.
Atropine Sulfate	0.0582 mg.
Hyoscine Hydrobromide	0.0195 mg.
Phenobarbital (¼ gr.)	48.6 mg.

Donnagesic No. 2 (red)

CODEINE Phosphate (1½ gr.)	97.2 mg.
Hyoscyamine Sulfate	0.3111 mg.
Atropine Sulfate	0.0582 mg.
Hyoscine Hydrobromide	0.0195 mg.
Phenobarbital (¼ gr.)	48.6 mg.

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Robins

A. H. ROBINS CO., INC.
RICHMOND 20, VIRGINIA
Ethical Pharmaceuticals of Merit Since 1878

*TM Reg. U.S. Pat. Off.—pat. applied for

It's a date—

...among other things...which distinguishes Vi-Penta Drops 'Roche.' Since all multivitamin solutions tend to lose strength in time, Vi-Penta® Drops are dated to assure full label potency. Just 0.6 cc daily provides required amounts of A, C, D and B vitamins (including B_6), and you'll find that both mothers and youngsters like them because they're easy to give and easy to take... Hoffmann - La Roche Inc.

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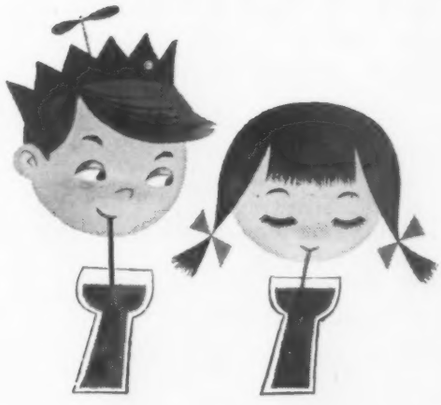

BRING YOUR PATIENT'S HIDDEN INFLAMMATION TO LIGHT WITH

C·R·P·A®

(C-reactive Protein Antiserum, Schieffelin)

- **C-Reactive protein in serum only when inflammation exists.**
- **Unlike E.S.R., no "Normal" range... either negative or positive.**
- **No false positives.**
- **Simpler . . . faster . . . more reliable aid to diagnosis.**
- **Quantity of precipitate reflects severity of condition . . . Precipitate diminishes as therapy reduces inflammation.**

Both venous blood and blood obtained by the "finger tip technique" (punctured as for blood count) can be used with equally reliable results. To make the test procedure fast and convenient a new compact C.R.P.A. Test Kit is now available; it contains C.R.P.A., CRP-Positest control solution, capillary tubes, test rack, and illustrated directions.

COMPLETE LITERATURE ON C.R.P.A. IN DETECTION OF RHEUMATIC DISEASES, MYOCARDIAL INFARCTION, AND MANY OTHER DISEASE STATES ON REQUEST.

Supplied:
TEST KIT *(For the complete procedure)*
C.R.P.A. . . . 1 ml. vials (80-110 determinations)
CRP-POSITEST* . . . 0.5 ml. vials
(Standardized test-control solution of C-Reactive Protein)
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CAPILLARY TUBES
(Two sizes) . . . 0.8 mm ID – 1.5 mm ID
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criteria for skeletal muscle relaxant

"The need for a therapeutic agent that would provide prolonged relaxation of spastic or rigid muscles is generally recognized. To date, there has been no available drug proved sufficiently safe, effective, or long-lasting to justify its general use."[1]

Before Flexin

NOW

flexin*

(Zoxazolamine,† McNeil)

fulfills these

supplied: 250 mg. yellow, scored tablets, bottles of 50.

(1) Abrahamsen, E. H., and Baird, H. W., III: J.A.M.A. *160*:749 (Mar. 3) 1956.

(2) Amols, W.: J.A.M.A. *160*:742 (Mar. 3) 1956.

(3) Rodriguez-Gomez, M.; Valdes-Rodriguez, A., and Drew, A. L.: J.A.M.A. *160*:752 (Mar. 3) 1956.

(4) Smith, R. T.; Kron, K. M.; Peak, W. P., and Hermann, I. F.: J.A.M.A. *160*:745 (Mar. 3) 1956.

*T.M. †U. S. Patent Pending

FLEXIN is sufficiently safe

"No significant alterations of pulse, blood pressure, or respiration were observed [during therapy with FLEXIN], and there were no deleterious effects noted in blood counts, urinalyses, or liver and kidney function tests."[2]

"...no important signs of toxicity were found in blood or urine studies...drowsiness and transient dizziness in an occasional patient, together with occasional mild gastric irritation, were the only undesirable side-effects observed..."[3]

FLEXIN is effective

"When it [FLEXIN] was administered orally in doses of 250 to 500 mg. three and four times a day, 14 of 18 patients with spasticity due to spinal cord lesions showed objective improvement of spasticity."[3]

"Rheumatic diseases with the major disability caused by stiffness and aching appear to respond well..."[4]

FLEXIN has a long duration of action

"The administration of an effective dose of zoxazolamine [FLEXIN] was usually followed by muscular relaxation within an hour, with the peak effect being reached within two hours and waning within four hours. Some degree of muscular relaxation was occasionally seen 24 hours or longer after discontinuance of therapy."[1]

requirements

McNEIL LABORATORIES, INC · PHILADELPHIA 32, PA. McNEIL

gentle

is the word

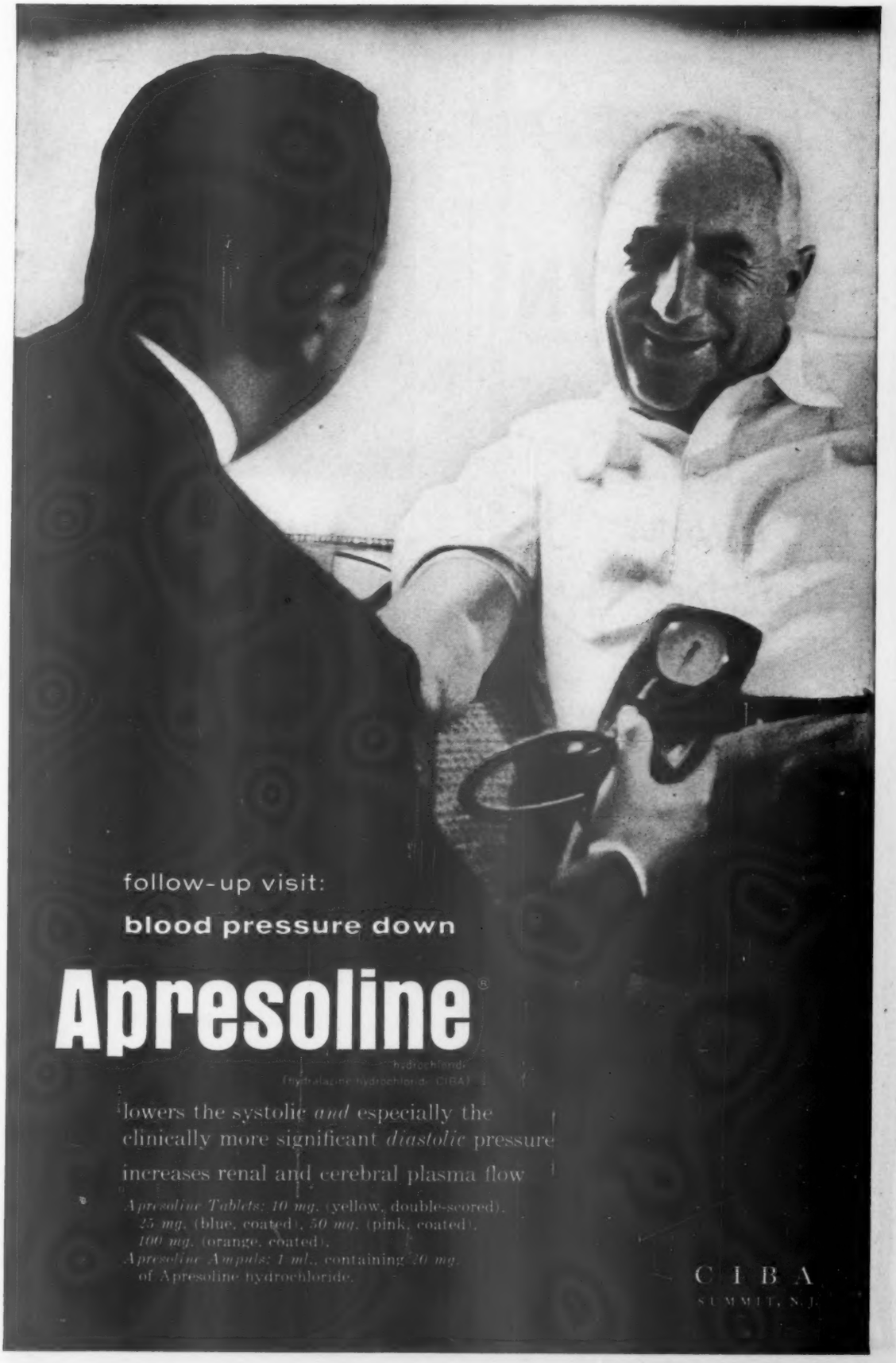
for Noludar

Mild, yet positive in action, Noludar 'Roche' is especially suited for the tense patient who needs to relax and remain clear-headed—or for the insomniac who wants a refreshing night's sleep without hangover. Not a barbiturate, not habit-forming. Tablets, 50 and 200 mg; elixir, 50 mg per teasp.

Noludar® brand of methyprylon
(3,3-diethyl-5-methyl-
2,4-piperidinedione)

ROCHE

Original Research in
Medicine and Chemistry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blood pressure down
Apresoline®
hydrochlend
(hydralazine hydrochloride CIBA)
lowers the systolic *and* especially the clinically more significant *diastolic* pressure
increases renal and cerebral plasma flow
Apresoline Tablets: 10 mg. (yellow, double-scored), *25 mg.* (blue, coated), *50 mg.* (pink, coated), *100 mg.* (orange, coated).
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CIBA
SUMMIT, N.J.

The Well-Proportioned Nutrients in Enriched Bread

Equally Important in LOW-RESIDUE DIETS

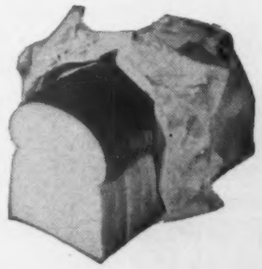
ENRICHED BREAD, plain or toasted, constitutes a nutritionally valuable component of the low-residue diet often prescribed in various gastrointestinal affections and following surgery on the gastrointestinal tract. In such conditions it is particularly necessary to provide adequate nutrition within the framework of a diet low in irritating substances.

The added nutrients in enriched bread are selected qualitatively and quantitatively because of their importance in everyday nutrition. They have proved equally advantageous when dietary adjustment is indicated for therapeutic purposes.

Enriched bread is nonirritating chemically as well as mechanically. It is free from bran and contains only negligible amounts (0.2 per cent) of soft cellulosic material. Its taste appeal is no less important than its open texture, its blandness, its easy digestibility.

The ready absorption of the balanced nutrients of enriched bread implements the utilization of its important amounts of protein, B vitamins, and minerals.

On the average, six slices of enriched bread (containing 4 per cent added nonfat milk solids), provide 12 grams of good quality protein (flour protein supplemented with milk protein), 0.36 mg. of thiamine, 0.26 mg. of riboflavin, 3.35 mg. of niacin, 3.5 mg. of iron, and 126 mg. of calcium.



AMERICAN BAKERS ASSOCIATION
20 NORTH WACKER DRIVE • CHICAGO 6, ILLINOIS

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

NEW

ATARAXOID is a unique, new combination of STERANE and ATARAX, which now permits simultaneous symptomatic control and reduction of attendant anxiety and apprehension in rheumatoid arthritis and other indications.

The added tranquilizer control, desirably easing mental stress, also directly assists clinical progress. It minimizes the chance of exacerbation related to emotional strain and facilitates patient confidence and cooperation in the therapeutic program toward maximum rehabilitation.

ATARAXOID exerts the anti-rheumatic, anti-inflammatory activity of STERANE distinctly superior to previous steroids, effective in radically reduced dosage, and with minimal disturbance of electrolyte and fluid metabolism.

The ataractic effect is a central neuro-relaxing action – the result of a marked cerebral specificity – free of mental fogging and devoid of any major complications: no liver, blood or brain damage. This peace-of-mind component is also used in the lowest dosage range.

Supplied: Each green, scored, ATARAXOID oral tablet contains 5 mg. prednisolone (STERANE) and 10 mg. hydroxyzine hydrochloride (ATARAX). Bottles of 30 and 100.

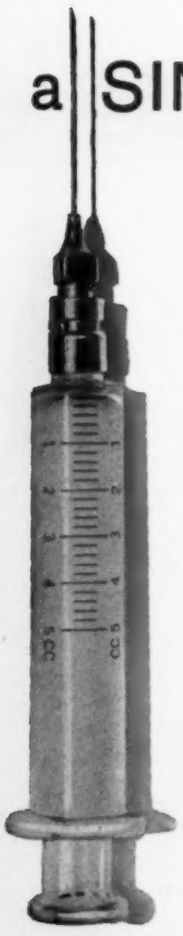
PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, New York

treat adrenocortical insufficiency

without the
difficulties
of
implants

without the
unpleasantness
of daily
injections

with a SINGLE injection a month



Percorten®

trimethylacetate

(desoxycorticosterone trimethylacetate CIBA)

Percorten trimethylacetate, developed after more than 3 years of research by CIBA, provides expedient, lasting hormonal support for the patient with adrenocortical hypofunction . . . avoiding both the uncertainty of surgical implantation and the vexation of daily injections. With once-a-month therapy, a single injection will produce prolonged activity without acute signs of overdosage.[1]

Multiple-dose Vials, 4 ml., containing 25 mg. Percorten trimethylacetate per ml. as an aqueous microcrystalline suspension for intramuscular use only.

1. Frawley, T. F., and Forsham, P. H.: J. Clin. Endocrinol. *11*:772 (July) 1951.

CIBA
SUMMIT, N. J.

for a sound sleep tonight,
a calm day tomorrow . . .

filmtab

Nembu-Serpin®

Nembu-Serpin delivers all of the tranquilizing-antihypertensive effect of reserpine—with this added advantage:

Patients experience almost immediate relief—calmer days, more restful nights—*beginning the very first day of Nembu-Serpin treatment.*

This faster onset of tranquilizing effect, produced by the synergistic action of Nembutal and reserpine, thus avoids prolonged waiting for a cumulative response to reserpine alone.

And fast-acting Nembu-Serpin makes lower reserpine dosages effective, side effects rare, medication economical. Combines 30 mg. Nembutal (pentobarbital) Calcium and 0.25 mg. reserpine. In bottles of 100 and 500 Filmtabs. Abbott

609215

®Filmtab—Film-sealed tablets

in acute and chronic pyelonephritis, cystitis and prostatitis

freedom

from pain, infection and resistant mutants

"Frequently, patients reported symptomatic improvement within 24 hours."[1] Furadantin "may be unique as a wide-spectrum antimicrobial that . . . does not invoke resistant mutants."[2]

Comparative Sensitivity to Furadantin of Infectious Microorganisms Isolated over a Two-Year Period[3]

Microorganism	Total no. strains	Sensitive*		Moderately sensitive*		Resistant*	
		No.	Per cent of total	No.	Per cent of total	No.	Per cent of total
Proteus vulgaris	237	209	88.2	28	11.8	0	0
Escherichia coli (including paracolon bacillus)	281	255	92.7	23	8.2	3	1.1
Aerobacter aerogenes	223	183	82.1	40	17.9	0	0
Streptococcus faecalis	160	155	96.7	5	3.1	0	0
Pseudomonas aeruginosa	101	5	5.0	40	39.9	56	55.4
Micrococcus pyogenes var. aureus	6	6	100	0	0	0	0
Klebsiella pneumoniae	3	3	100	0	0	0	0
Alcaligenes faecalis	2	2	100	0	0	0	0

*Organisms inhibited by 100 μg./ml. or less are classified as sensitive, by 200 to 400 μg./ml. as moderately sensitive, and those not inhibited by 400 μg./ml. as resistant.

"The status of P. vulgaris and of M. pyogenes var. aureus is especially noteworthy in the light of the high degree of resistance exhibited by those organisms to antibiotics currently employed."[3]

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Furadantin®

BRAND OF NITROFURANTOIN

FURADANTIN DOSAGE:
Average adult dose is 100 mg., q.i.d. (at mealtime, and on retiring, with food or milk). Average daily dosage for children is 5 to 7 mg./Kg. in four divided doses.

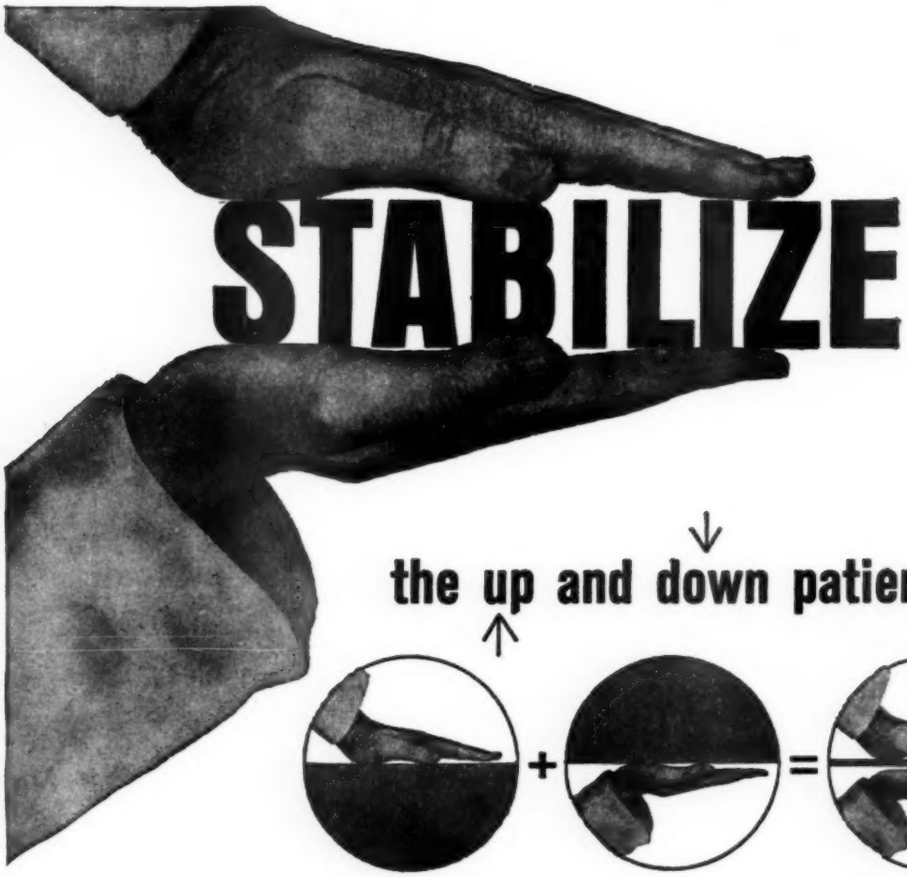
EATON LABORATORIES
Norwich New York

SUPPLIED:
Tablets, 50 and 100 mg., bottles of 25 and 100.
Oral Suspension, 5 mg., per cc., bottle of 118 cc.

NITROFURANS—a new class of antimicrobials—neither antibiotics nor sulfonamides

Advertisers Index

October, 1956



Serpasil
tranquilizer

Ritalin
psychomotor stimulant

Serpatilin
emotional stabilizer

To induce emotional equilibrium in those who swing from anxiety to depression, Serpatilin combines the relaxing, tranquilizing action of Serpasil with the mild mood-lifting effect of the new cortical stimulant, Ritalin. In recent months, numerous clinical studies have indicated the value of combining these agents for the treatment of various disorders marked by tension, nervousness, anxiety, apathy, irritability and depression. Arnoff,[1] in a study of 51 patients, found the combination of definite value in a variety of complaints, noting no effect on blood pressure or heart rate. Lazarte and Petersen[2] also found Serpatilin effective in counteracting the side effects of reserpine and chlorpromazine. They reported: "The stimulating effect of Ritalin seemed complementary to the action of reserpine . . . in that it brought forth a better quality of increased psychomotor activity."

1. Arnoff, B.: Personal communication. 2. Lazarte, J. A., and Petersen, M.C.: Personal communication.

Serpatilin Tablets, 0.1 mg./10 mg., each containing 0.1 mg. Serpasil® (reserpine CIBA) and 10 mg. Ritalin® hydrochloride (methyl-phenidylacetate hydrochloride CIBA).

Dosage: 1 tablet b.i.d. or t.i.d., adjusted to the individual.

CIBA
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Serpatilin T.M.

(reserpine and methyl-phenidylacetate hydrochloride CIBA)

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